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RISK OF MYOPATHY ASSOCIATED WITH THE USE OF STATINS AND POTENTIALLY INTERACTING MEDICATIONS: A RETROSPECTIVE ANALYSIS

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RISK OF MYOPATHY ASSOCIATED WITH THE USE OF STATINS AND POTENTIALLY INTERACTING MEDICATIONS: A RETROSPECTIVE ANALYSIS

by

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Dedication

To Mummy and Pappa to whom I owe everything I have learnt in life, and to my husband for his love, encouragement, and continuous support

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RISK OF MYOPATHY ASSOCIATED WITH THE USE OF STATINS AND POTENTIALLY INTERACTING MEDICATIONS: A RETROSPECTIVE ANALYSIS

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Statins are the most widely used drugs for the management of hyperlipidemia. Clinical trials have demonstrated the beneficial effects of statins in treatment of hyperlipidemia and in prevention of cardiovascular diseases. Statins as a class of drugs are generally well tolerated; however, statin-associated myopathy is a major clinical concern. The risk of myopathy further increases with concurrent use of statins with potentially interacting medications (PIMs). There is limited information on the risk of myopathy associated with the use of statins and PIMs.

The purpose of this study was to evaluate the risk and risk factors of myopathy in patients using statins with PIMs compared to those patients using statins without PIMs. The study was a retrospective cohort analysis using the Texas Medicaid database. The study population included patients who were new statin users between the ages of 21 and 64 years and were eligible for Texas Medicaid benefits between September 1, 1998 and

August 31, 2003. The main outcome measures were the incidence rates of myopathy per 100 person-months of treatment and the odds of developing myopathy.

In 8,822 eligible patients, 113 cases of myopathy occurred during an average follow-up of 3.9 months. The overall incidence of myopathy in the study population was 0.32 per 100 person-months. Patients using statins with PIMs had 2.7-fold (95% CI: 1.83–4.03) greater risk of developing myopathy than patients using statins without PIMs. In addition, increasing number of comorbidities was associated with 1.3 times (95%CI: 1.159-1.637) greater risk of myopathy. Also, the risk of myopathy decreased (OR: 0.997; 95% CI: 0.995-0.999) with increasing statin use.

The risk of myopathy was higher for patients using statins and PIMs as compared to patients using statins without PIMs. Health care professionals need to monitor patients closely when they use statins and PIMs concurrently, especially in patients with multiple comorbidities.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

According to the American Heart Association, 106.9 million Americans aged 20 years and older (50.7% of the United States population) had total cholesterol levels above 200 mg/DL, in 2002, mainly due to increase in low density lipoprotein cholesterol.[1] Statins or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are the most widely used drugs to treat elevated cholesterol. According to Med Ad News, the two top selling drugs are cholesterol lowering drugs (Lipitor® and Zocor®).[2] Cholesterol lowering drugs represent the second best therapeutics category by sales among the world's top 200 prescription drugs.[3]

Statins are shown to be highly effective in treating dyslipidemia and reducing the risk of cardiovascular events in primary and secondary prevention trials. Statins are considered as first-line of drug therapy. As a class of drugs, statins are generally well-tolerated; however, the major clinical concern related to statin therapy is myopathy. This was evident from the recent withdrawal of cerivastatin, which was withdrawn from the market in 2001 because of 31 deaths associated with drug-induced rhabdomyolysis.

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[1] Heart Disease and Stroke Statistics 2006 Update. Dallas: American Heart Association, 2006.
[2] Humphreys A, Mayer R. Med Ad News 200 - World's best-selling medicine. *Med Ad News* 2005;24:1-60.
[3] Ibid.

The clinical presentation of myopathy ranges in severity from simple myalgia to the most severe manifestation, rhabdomyolysis. The incidence of myopathy varies between 0.1 percent and 5.0 percent depending on dose and type of statin, and severity of the condition.[4] However, this risk increases with concurrent use of potentially interacting medications with statins.

Most statins are metabolized by the cytochrome P450 system, except pravastatin. This enzyme system is responsible for metabolism of many other pharmacologic agents. The combination of statins with other agents that inhibit the cytochrome P450 system increases the risk of myopathy. One study estimated the risk of myopathy to be 6-fold higher in patients who used potentially interacting medications with statins as compared with statin-only users.[5] There is very limited information on the magnitude of risk when statins are taken with potentially interacting medications.

The potential for statin-induced myopathy is becoming more of a concern as guidelines recommend more aggressive treatment of elevated cholesterol levels.[6] This means that the number of people who will be treated with higher statin doses and combination therapies will increase to meet the current guidelines. At the same time, patients with multiple medications due to comorbidities are also at an increased risk of myopathy. Given this scenario, it is important to identify patients who are at a higher risk of myopathy.

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[4] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

[5] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8, Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.

[6] Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.

The general purpose of this study was to estimate the risk of myopathy in Texas Medicaid patients and determine the risk factors for myopathy. By identifying the risk factors of myopathy, health care professionals will be better able to manage their patients with high cholesterol who are on multiple medications, and who have certain risk factors that predispose them to the risk of myopathy.

This chapter is divided into the following sections:

- General background on hyperlipidemia;
- Overview of statins;
- Background of myopathy;
- Statins and potentially interacting medications;
- Rationale of the study;
- Goals, objectives, and hypotheses of the study.

SECTION I

GENERAL BACKGROUND ON HYPERIPIDEMIA

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE

According to the American Heart Association, the prevalence of cardiovascular diseases (CVD) is 34.2% and the cost of CVD is $393.5 billion.[7] CVD is the leading cause of death in the United States.[8] Coronary heart diseases (CHD), which are also commonly referred to as coronary artery diseases (CAD), account for about half of all cardiovascular deaths in the U.S.[9] About 13.0 million people in the U.S. suffer from CHD. A majority of these patients suffer from myocardial infarction (MI) or angina pectoris. It is estimated that the incidence of new MI is 565,000 and that of angina pectoris is 400,000 annually.[10] This poses a significant burden on the society in terms of the use of health care resources and cost. About 90% of the CHD patients have at least one of the following major risk factors: hypertension, high cholesterol, current smoker or diabetes.[11] According to a study conducted in 52 countries, nine risk factors including cigarette smoking, abnormal lipid levels, hypertension, diabetes, abdominal obesity, a lack of physical activity, low daily fruit and vegetable consumption, alcohol overconsumption, and psychosocial factors (e.g. depression, perceived stress) account for

[7] Heart Disease and Stroke Statistics 2006 Update. Dallas: American Heart Association, 2006.
[8] Ibid.
[9] Ibid.
[10] Ibid.
[11] Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA* 2003;290:891-7.

over 90% of the risk of an initial MI.[12] Controlling these risk factors or modifying them altogether can decrease the risk of CHD. One of the most important risk factors to control is abnormal level of lipids or hyperlipidemia. The next section presents information on hyperlipidemia, its prevalence and association with CHD.

BACKGROUND ON HYPERLIPIDEMIA AND ITS ASSOCIATION WITH CHD

Hyperlipidemia (which is also commonly referred to as dyslipidemia or hypercholesterolemia), is defined as an elevation of lipid levels in the blood plasma. Lipoproteins are responsible for the transport of lipids, mainly triglycerides (TG) and cholesterol, through the plasma. The four main classes of lipoproteins are high-density lipoproteins (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and chylomicrons. Another class, intermediate density lipoprotein (IDL) resides between VLDL and LDL. The amount of TG and cholesterol carried by each lipoprotein is variable. For example, VLDL and chylomicrons are rich in TG and LDL is a carrier for cholesterol.[13] Apolipoproteins (Apo) are the protein constituents of these lipoproteins. Their main function is to regulate enzymes and bind to receptors thereby controlling lipid metabolism.

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[12] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-52.

[13] Gaw A. Hyperlipidemia as a risk factor for vascular disease. In: Gaw A, Packard C J, Shepherd. J, eds. Statins : the HMG-CoA reductase inhibitors in perspective. London, New York: Martin Dunitz ; Independence, KY, 2004:1-18.

LDL cholesterol makes up 60 to 70% of total serum cholesterol. The National Cholesterol Education Panel (NCEP) recognizes it as the primary target for lipid lowering therapies.[14] Other targets include triglycerides and HDL cholesterol levels.

Studies such as the Framingham Heart Study,[15] the Multiple Risk Factor Intervention Trial (MRFIT),[16] and the Lipid Research Clinics Primary Prevention Trial (LRCPPT)[17] have shown a positive strong correlation between LDL cholesterol levels and the risk of CHD among men and women initially free of CHD. These studies have provided evidence that LDL is an important risk factor for CHD. Similarly, recent published meta-analyses found that elevated triglycerides were associated with an increase in cardiovascular risk.[18,19] Results of Framingham study have also shown a negative association between HDL cholesterol levels and the occurrence of CHD.[20] A review of trials by Boden et al. has shown a similar inverse relationship between HDL cholesterol and the risk of CHD.[21] In summary, all of these trials provide evidence that

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[14] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.

[15] Castelli WP, Anderson K, Wilson PW, et al. Lipids and risk of coronary heart disease. The Framingham Study. *Ann Epidemiol* 1992;2:23-28.

[16] Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986;256:2823-8.

[17] Lipid Research Clinic Program Group. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 1984;251:365-74.

[18] Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol* 1998;81:7B-12B.

[19] Assmann G, Schulte H, Funke H, et al. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. *Eur Heart J* 1998;19:M8-14.

[20] Castelli WP, Anderson K, Wilson PW, et al. Lipids and risk of coronary heart disease. The Framingham Study. *Ann Epidemiol* 1992;2:23-28.

[21] Boden WE. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: Assessing the data from the Framingham to the Veterans Affairs High-density Lipoprotein Intervention Trials. American Journal of Cardiology 2000; 86 (Suppl 12A): 19L-22L.

there is an increased risk of CHD with an increase in LDL and TG levels, and a decrease in HDL levels.

PRIMARY AND SECONDARY CAUSES OF HYPERLIPIDEMIA

The primary cause of hyperlipidemia is the underlying metabolic defects, which have a genetic basis. Primary hyperlipidemias include familial or polygenic hypercholesterolemia, familial combined hyperlipidemia, familial hypertriglyceridemia and rare dyslipidemia's such as dysbetalipoproteinemia.[22] The Fredickson/World Health Organization classification of lipoprotein phenotype (i.e. lipoprotein I, IIa, IIb, III, IV and V) is used to distinguish the many different types of hyperlipoproteinemia.[23] Types I and V are rare while types IIa, IIb, III and IV are more common. This classification is widely used and gives guidance for cholesterol management.

Secondary causes of hyperlipidemia are related to disease risk factors and drugs associated with hyperlipidemia. Disease risk factors include diabetes, obesity, hypothyroidism, and post-renal transplantation. Drug risk factors include steroids, diuretics, beta-blockers and immunosuppressants. In addition, diet is also a significant risk factor contributing to hyperlipidemia.[24] Given so many causes of hyperlipidemia, the prevalence of hyperlipidemia is large in the population.

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[22] Farnier M, Davignon J. Current and future treatment of hyperlipidemia: the role of statins. *Am J Cardiol* 1998;82:3J-10J.
[23] Ibid.
[24] Gaw A. Hyperlipidemia as a risk factor for vascular disease. In: Gaw A, Packard C J, Shepherd. J, eds. Statins : the HMG-CoA reductase inhibitors in perspective. London, New York: Martin Dunitz ; Independence, KY, 2004:1-18.

PREVALENCE OF HYPERLIPIDEMIA

According to the NCEP guidelines for cholesterol management, a total cholesterol level of 200 to 239 mg/dl is considered borderline high and above 240 mg/dl is considered high. Similarly, LDL above 130 mg/dl is considered high and HDL below 40mg/dl is considered low.[25] Based on this classification, in 2002, there were about 106.9 million adults who had total cholesterol of 200 mg/dl or higher, 95 million who had LDL greater than 130 mg/dl and 54.7 million who had HDL lower than 40 mg/dl.[26]

A comparison of data from the National Health and Nutrition Examination Surveys (NHANES) 1999-2000 to NHANES 1988-1994 showed no statistically or clinically significant change in mean cholesterol levels over the ten-year period.[27] This lack of change in cholesterol levels occurred despite a modest increase in use of lipid lowering drugs. Although, there has been a decreasing trend in elevated cholesterol levels since 1980, this decrease has become smaller over the years. This may be due to the large number of eligible people who may not be receiving dietary or pharmacological interventions. NCEP has developed guidelines for cholesterol testing and management.

NATIONAL CHOLESTEROL EDUCATION PANEL GUIDELINES

The NCEP expert panel on detection, evaluation, and treatment of high blood cholesterol in adults examines the available evidence on CHD and high cholesterol,

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[25] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.

[26] Heart Disease and Stroke Statistics 2006 Update. Dallas: American Heart Association, 2006.

[27] Ford ES, Mokdad AH, Giles WH, et al. Serum total cholesterol concentrations and awareness, treatment, and control of hypercholesterolemia among US adults: findings from the National Health and Nutrition Examination Survey, 1999 to 2000. *Circulation* 2003;107:2185-9.

identifies relevant issues, and develops guidelines for physicians and other heath care providers. Since 1987, three sets of guidelines have been issued for management of cholesterol.

The Adult Treatment Panel I (ATP I) provided a strategy for primary prevention of CHD in persons with LDL levels between 130 and 159 mg/dl, in persons with LDL levels greater than 160 mg/dl and those with multiple (>2) risk factors. ATP II reemphasized the importance of primary prevention and also added the need for intensive management of LDL cholesterol in persons with established CHD. The core of ATP III is based on ATP I and ATP II; however, the focus of these guidelines is on primary prevention in persons with multiple risk factors.[28]

The following are some of the new features of ATP III guidelines:[29]

- LDL cholesterol levels less than 100 mg/dl are optimal;
- HDL cholesterol levels should be greater than 40 mg/dl (compared to greater than 35 mg/dl in earlier reports) because this cut off is a better measure of depressed HDL;
- The triglyceride cutpoints were lowered to give more attention to moderate elevations;
- Persons with diabetes without CHD, most of whom have multiple risk factors, have the same risk as patients who are CHD risk equivalent. (CHD risk equivalents are persons that have clinical forms of atherosclerotic disease other

[28] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
[29] Ibid.

than CHD, or have diabetes or multiple risk factors with 10-year risk for CHD greater than 20%);

- Patients with multiple risk factors are identified for more intensive treatment using Framingham projections of 10-year absolute risk reduction;
- Patients with metabolic syndrome are identified as candidates for intensified therapeutic lifestyle changes (TLC);
- A complete lipoprotein profile is the preferred initial test rather than screening for total cholesterol and HDL alone;
- The use of plant stanols/sterols and viscous fiber is encouraged as dietary therapy to enhance lowering of LDL cholesterol;
- Strategies are provided to promote adherence to therapeutic lifestyle changes and drug therapies; and
- Persons with triglycerides greater than 200 mg/dl should be treated beyond lowering LDL levels.

Recently, Ford et al.[30] established the distribution of the 10-year risk for CHD among U.S. adults using the NCEP ATP III algorithm. Based on this data, there were about 23 million (15. 5%) adults at moderate risk, and about 4 million (2.9%) adults at high risk as defined by ATP III guidelines. This risk varied with age and sex. The percent of people with high risk increased with age and was higher for men compared to women. A large number of this population would then be eligible for some kind of intervention to reduce

[30] Ford ES, Giles WH, Mokdad AH. The distribution of 10-Year risk for coronary heart disease among US adults: findings from the National Health and Nutrition Examination Survey III. *J Am Coll Cardiol* 2004;43:1791-6.

LDL levels. Table 1.1 defines LDL cholesterol levels and cutpoints for initiation of TLC and drug therapies.

Table 1.1: LDL cholesterol goals and cutpoints for therapeutic lifestyle changes and drug therapy in different risk categories based on ATP III

Risk Category	LDL Goal (mg/dL)	LDL level at which to initiate Therapeutic Lifestyle Changes (mg/dL)	LDL level at which to consider drug therapy (mg/dL)
CHD or CHD equivalents (10 year risk >20 %)	<100	≥100	≥130
>2 risk factors (10 year risk ≤ 20 %)	<130	≥130	10-year risk 10 to 20 %: ≥ 130, 10-year risk<10 %: ≥160
0 to 1 risk factors	< 160	≥160	≥190 (160 to 189: drug optional

Source: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.

Based on these NCEP guidelines, an estimated 36 million Americans are eligible for drug therapy, of which 32% will be under the age of 45 and 27% will be above 65 years of age.[31,32] This represents a 140% increase in the overall eligibility as compared to

[31] Hoerger TJ, Bala MV, Bray JW, et al. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *Am J Cardiol* 1998;82:61-5.
[32] Fedder DO, Koro CE, L'Italien GJ. New National Cholesterol Education Program III guidelines for primary prevention lipid-lowering drug therapy: projected impact on the size, sex, and age distribution of the treatment-eligible population. *Circulation* 2002;105:152-6.

ATP II guidelines. In summary, a significant number of people require some kind of management of hyperlipidemia.

MANAGEMENT OF HYPERLIPIDEMIA

The two main approaches to the management of hyperlipidemia, as stated in the NCEP guidelines are therapeutic lifestyle changes and drug therapy.

Therapeutic lifestyle changes for management of hyperlipidemia

The first step in TLC for management of hyperlipidemia includes dietary management. ATP III guidelines recommend a reduced intake of saturated fats and cholesterol to reduce LDL levels. In addition, a higher intake of total fat (mostly unsaturated fat) can help to reduce triglycerides and raise HDL levels. Also, moderate physical activity and weight reduction (in case of obese patients) is recommended along with dietary changes. ATP III recommends changes in lifestyle to lower lipid levels before initiating drug therapy.[33]

Drug therapy for management of hyperlipidemia

A large portion of the population who have high short-term and long-term risk for CHD will need drug therapy along with TLC. This is based on the NCEP cutpoints for drug therapy (Table 1.1). The most important drugs for lowering blood cholesterol

[33] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.

include bile acid sequestrants, niacin, cholesterol absorption inhibitors, hormone replacement therapy (HRT), fibrates, and statins. These drugs are described in detail, especially statins which is the focus of this dissertation.

BILE ACID RESINS

The agents in this class include cholestyramine, colestipol and colesevelam. These drugs act by interrupting the enterohepatic circulation of bile acids by binding them in the intestine to form an insoluble complex that is excreted in the feces.[34] Due to depletion in bile acids, their hepatic synthesis is increased, which results in the increased transport of cholesterol to liver and decreased levels of serum cholesterol.[35] In some persons, bile acid resins increase the VLDL levels, thereby raising serum triglyceride levels.[36,37]

The major action of bile acid sequestrants is to lower LDL cholesterol. These drugs reduce the LDL cholesterol by 15 to 30%, increase HDL cholesterol by 3 to 5% and they have no effect or slight increase on triglyceride levels.[38] In the Lipid Research Clinics Primary Prevention Trial, treatment with cholestyramine reduced the risk of

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[34] Davidson MH, Dillon MA, Gordon B, et al. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 1999;159:1893-900.

[35] Shepherd J. Mechanism of action of bile acid sequestrants and other lipid-lowering drugs. *Cardiology* 1989;76 Suppl 1:65-71; discussion 71-4.

[36] Beil U, Crouse JR, Einarsson K, et al. Effects of interruption of the enterohepatic circulation of bile acids on the transport of very low density-lipoprotein triglycerides. *Metabolism* 1982;31:438-44.

[37] Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999;341:498-511.

[38] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.

CHD.[39] In addition, bile acid resins in combination with other lipid lowering drugs enhances the lipid lowering effects of these drugs.[40,41,42]

The main disadvantage of bile acid sequestrants is gastrointestinal side effects. These include bloating, abdominal discomfort, nausea, constipation and dyspepsia.[43] Colesevelam has fewer side effects than the other drugs.[44] In addition, concurrent administration of bile acid resins with digitalis, thiazide diuretics, beta-blockers, warfarin and exogenous thyroid hormones increases the absorption of the latter drugs.[45]

NIACIN

Niacin is a cholesterol-lowering drug that reduces LDL and triglyceride levels and increases HDL levels.[46] It modifies lipid levels by inhibiting lipoprotein synthesis and reducing the production of VLDL particles by the liver through reduced transport of free fatty acids to the liver.[47]

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[39] Lipid Research Clinic Program Group. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-64.
[40] Blankenhorn DH, Nessim SA, Johnson RL, et al. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;257:3233-40.
[41] The Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. *JAMA* 1988;260:359-66.
[42] Pravastatin Multicenter Study Group II. Comparative efficacy and safety of pravastatin and cholestyramine alone and combined in patients with hypercholesterolemia. *Arch Intern Med* 1993;153:1321-9.
[43] Kreisberg RA, Oberman A. Medical management of hyperlipidemia/dyslipidemia. *J Clin Endocrinol Metab* 2003;88:2445-61.
[44] Davidson MH, Dillon MA, Gordon B, et al. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 1999;159:1893-900.
[45] Cziraky M. Clinical positioning of HMG-CoA reductase inhibitors in lipid management protocols. *Pharmacoeconomics* 1998;14:29-38.
[46] Kreisberg RA, Oberman A. Medical management of hyperlipidemia/dyslipidemia. *J Clin Endocrinol Metab* 2003;88:2445-61.
[47] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.

Niacin decreases LDL levels by 5 to 15%, triglyceride levels by 20 to 50% and increases HDL levels by 15 to 35%.[48] In a meta-analysis conducted to evaluate the safety and efficacy of niacin, it was shown that niacin was associated with a 20% decrease in triglycerides, a 12% decrease in LDL levels and a 16% increase in HDL levels.[49] Niacin was shown to decrease the risk of recurrent myocardial infarction in the Coronary Drug Project, [50]and the total mortality in patients who had received niacin was reduced in a 15-year follow-up.[51]

The major disadvantages of niacin therapy relate to its side effects. These include flushing, itching, headache, fatigue and gastrointestinal symptoms such as nausea, dyspepsia, flatulence, vomiting, diarrhea and activation of peptic ulcer may occur. Other major side effects include hepatotoxicity, hyperuricemia and gout, and hyperglycemia. These risks are increased at higher doses and the risk of hepatotoxicity is increased with sustained released preparations (except Niaspan).[52] The use of niacin with statin therapy has been cautioned due to case reports of myopathy (discussed later).[53] Although efficacious, the long-term use of these drugs has been limited due to side effects.

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[48] Ibid.

[49] Birjmohun RS, Hutten BA, Kastelein JJ, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005;45:185-97.

[50] Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;231:360-81.

[51] Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986;8:1245-55.

[52] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.

[53] Reaven P, Witztum JL. Lovastatin, nicotinic acid, and rhabdomyolysis. *Ann Intern Med* 1988;109:597-8.

CHOLESTEROL ABSORPTION INHIBITORS

Ezetimibe is the first cholesterol absorption inhibitor approved by FDA in November 2002. It blocks reabsorption of cholesterol secreted into bile, and the enterohepatic circulation of endogenously produced cholesterol. The reduction in LDL is due to increased endogenous catabolism of LDL.[54]

Ezetimibe has been shown to reduce LDL levels by 15 to 20% with trivial effects on triglycerides and HDL levels.[55] Ezetimibe in combination with statins are highly effective in controlling lipid levels.[56,57] It can be used as an adjunct in persons whose LDL levels are not well controlled with statins. However, its effects on cardiovascular endpoints are not known. There has been one case-report in the literature in which patients developed myopathy after ezitimibe was added to the statin therapy.[58] This drug will have to be continuously monitored for long-term effects.

HORMONE REPLACEMENT THERAPY

In a study conducted on Framingham cohort of women, it was shown that postmenopausal women had two to six times greater incidence of CVD as compared to pre-menopausal women.[59] This may be because of the artherogenic changes in plasma

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[54] Kreisberg RA, Oberman A. Medical management of hyperlipidemia/dyslipidemia. *J Clin Endocrinol Metab* 2003;88:2445-61.
[55] Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1092-7.
[56] Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;40:2125-34.
[57] Gagne C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1084-91.
[58] Fux R, Morike K, UF G. Ezitimibe and statin-associated myopathy. *Ann Intern Med* 2004;140:671.
[59] Kannel WB, Hjortland MC, McNamara PM, et al. Menopause and risk of cardiovascular disease: the Framingham study. *Ann Intern Med* 1976;85:447-52.

lipid levels associated with estrogen deficiency.[60] These changes can be avoided with the use of hormone replacement therapy (HRT). However, there is considerable controversy and confusion over the use of HRT to reduce CHD risk in postmenopausal women. There has been discrepancy in the results of observational studies and controlled trials.

The Nurses Health Study,[61] an observational study, suggested that there was a beneficial effect of estrogen replacement on CAD as well as a significant reduction in the probability of CAD events for women who were on estrogen replacement therapy. In contrast, the Heart and Estrogen/Progesterone Replacement Study (HERS),[62] a secondary prevention trial, indicated that estrogen plus progestin therapy did not reduce the overall risk of MI or death from CHD. Further analysis showed that the combination therapy increased the risk of CHD events in the first year, which reduced significantly in the following years. More recently, the Women's Health Initiative (WHI) study,[63] a randomized controlled trial, showed a small but significant increase in the risk of CHD in women using HRT. As can be seen from the above evidence, there is a lot of uncertainty in the use of HRT for prevention of CHD. The ATP III does not recommend the use of HRT in prevention of CHD in postmenopausal women.[64]

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[60] Warren MP, Halpert S. Hormone replacement therapy: controversies, pros and cons. *Best Pract Res Clin Endocrinol Metab* 2004;18:317-32.

[61] Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-61.

[62] Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605-13.

[63] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.

[64] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.

FIBRATES

Three fibrates are currently available in the U.S.: gemfibrozil, fenofibrate, and clofibrate. In addition, bezafibrate and ciprofibrate are available outside the U.S. Fibrates are mainly used in the reduction of triglycerides, although they have a mild effect on LDL levels.[65]

Mechanism of Action

The mechanism of action of fibrates is complex and there may be some variation in this class. They have an effect on lipoprotein lipase, which increases the catabolism of triglyceride rich lipoprotein thereby decreasing triglyceride levels. Triglyceride levels are also decreased due to increased fatty acid oxidation that reduces the formation of VLDL triglycerides. Fibrates also increase the production of apolipoprotein A (apoA) I and apoA II, which contribute to an increase in HDL levels.[66] Recent research has shown that all these activities are due to stimulation of peroxisome proliferator activator receptor alpha. Through this mechanism, the activity of apoA I, fatty acid transport protein, fatty acid oxidation, and possibly lipoprotein lipase are upregulated by fibrates.[67,68] In

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[65] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.

[66] Staels B, Dallongeville J, Auwerx J, et al. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* 1998;98:2088-93.

[67] Schoonjans K, Staels B, Auwerx J. Role of the peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. *J Lipid Res* 1996;37:907-25.

[68] Kreisberg RA, Oberman A. Medical management of hyperlipidemia/dyslipidemia. *J Clin Endocrinol Metab* 2003;88:2445-61.

addition, triglyceride lowering transforms small dense LDL into normal sized LDL, thereby increasing resistance of LDL to oxidation.[69]

As mentioned earlier the primary indication for fibrates is lowering of triglycerides levels. Many trials have been conducted to evaluate the efficacy of fibrates on lipid levels.

Efficacy of fibrates

Recently, Birjmohun et al.[70] published a meta-analysis evaluating the effects of fibrates. This study evaluated 53 trials that compared fibrates with placebo. According to the study, the use of fibrates caused a decrease of 36% in TG levels, a decrease of 8% in LDL levels, and an increase of 10% in HDL levels. The effects varied between fibrates with gemfibrozil having the greatest effect on reduction of TG (48%). Most trials showed a reduction in LDL; however, some trials did show an increase or unchanged levels of LDL. Most trials showed an increase in HDL levels except clofibrate trials, which showed a decrease in HDL levels. The increase in HDL levels was more profound in patients having combined hyperlipidemia and/or hypercholesterolemia.[71] These results are consistent with the NCEP guidelines.[72]

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[69] Staels B, Dallongeville J, Auwerx J, et al. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* 1998;98:2088-93.

[70] Birjmohun RS, Hutten BA, Kastelein JJ, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005;45:185-97.

[71] Ibid.

[72] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.

The studies evaluating the effect of fibrates on CV outcomes are limited. Therapy with gemfibrozil reduced the risk of MI in both primary and secondary prevention trials, and reduced the risk of CHD events and stroke in secondary prevention trial.[73,74] Clofibrate also has been shown to reduce the risk of MI in primary prevention trial;[75] however, these beneficial effects have not been shown in all clinical trials.[76,77] With the exception of Veterans Administration HDL Intervention Trial (VA-HIT),[78] no other trials have shown a reduction in risk of CHD death. In fact, in the WHO Clofibrate Study,[79] total mortality was significantly greater in the clofibrate group due to increased number of non-CHD deaths. Based on the above evidence, the effect of fibrates on CV outcomes and mortality are inconsistent.

Safety of fibrates

Fibrates are generally well tolerated; the most common side effects are skin reactions and gastrointestinal side-effects. In a meta-analysis conducted by Birjmohun et

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[73] Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-45.

[74] Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410-8.

[75] Report from the Committee of Principal Investigators. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 1978;40:1069-118.

[76] Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;231:360-81.

[77] The Bezafibrate Infarction Prevention (BIP) Study. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. *Circulation* 2000;102:21-7.

[78] Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410-8.

[79] Report from the Committee of Principal Investigators. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 1978;40:1069-118.

al.,[80] the incidence of adverse effects was 33% in the fibrate group versus 30% if the placebo group. Besides the above-mentioned side effects, the other adverse reactions that occurred less frequently included hepatoxicity and musculoskeletal symptoms. There was no statistically significant difference in the number of musculoskeletal symptoms experienced by the treatment group versus the placebo group (relative risk (RR): 1.23; 95% confidence interval (CI): 0.65-2.32, p=0.52).[81] The risk of musle-related events is increased in persons suffering from renal failure. In spite of low reporting of myopathy in clinical trials, there have been case-reports of myopathy published in the literature related to use of fibrates.

Case-reports and incidence of muscle-related events

Acute rhabdomyolysis had been reported during treatment with ciprofibrate,[82] gemfibrozil,[83,84] fenofibrate,[85,86] clofibrate,[87] and bezafibrate.[88] Alseikh-Ali et al.[89] reviewed the adverse events reported to the FDA in which gemfibrozil or fenofibrate was

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[80] Birjmohun RS, Hutten BA, Kastelein JJ, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005;45:185-97.
[81] Ibid.
[82] Giraud O, Chanu B, Farge D, et al. Acute rhabdomyolysis associated with digestive disorders during an overdoes of ciprofibrate. *Gastroenterol Clin Biol* 1995;19:231-232.
[83] Magarian GJ, Lucas LM, C C. Gemfibrozil-induced myopathy. *Arch Intern Med* 1991;151:1873-1874.
[84] Gorriz JL, Sancho A, JM L-M. Rhabdomyolysis and acute renal failure associated with gemfibrozil. *Nephron* 1996;74:437-438.
[85] Clouatre Y, Leblanc L, D O. Fenofibrate-induced rhabodmyolysis in two dialysis patients with hyopthyroidism. *Nephrol Dial Transplant* 1999;14:1047-48.
[86] Barker BJ, Goodenough BB, JM F. Fenofibrate monotherapy induced rhabdomyolysis. *Diabetes Care* 2003;26:2482-83.
[87] Muscari A, Puddu GM, Puddu P. Lipid-lowering drugs: Are adverse effects predictable and reversible? *Cardiology* 2002;97:115-121.
[88] Ibid.
[89] Alsheikh-Ali Alawi A., Kuvin J T., H. KR. Risk of adverse events with fibrates. *Am J Cardiol* 2004;94:935-38.

the suspected cause of the adverse event. Rates of muscle-related events without rhabdomyolysis were 15.7 per million prescriptions of gemfibrozil versus 8.8 per million prescriptions of fenofibrate. Rates of rhabdomyolysis were even higher (59.6 per million prescriptions of gemfibrozil versus 5.5 million prescriptions or fenofibrate). In an epidemiologic study, the relative risk of myopathy for fibrate users was 42.2 as compared to non-users and 5.5 as compared to statin users.[90] In another study, the average incidence of myopathy was estimated to be 2.82 per 10,000 person years.[91]

In summary, there is inconsistency in reported rates of myopathy related to use of fibrates. However, it appears that the risk of myopathy is greater with fibrates than with statins. Therefore, the use of statins and fibrates together may further increase the risk of myopathy, which can lead to rhabdomyolysis. A discussion on studies evaluating safety of combination statin-fibrate therapy will be presented later. Caution is needed when using these two drugs together.

The next section describes statins in the management of hyperlipidemia, which is the primary focus of this dissertation. This section is divided into the following sections:

- History and chemistry of statins;
- Pharmacokinetics and mechanism of action;
- Primary and secondary prevention trials; and
- Safety and tolerability of statins.

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[90] Gaist D, Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565-9.

[91] Graham D. J., Staffa J. A., Shatin D., et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.

SECTION II

OVERVIEW OF STATINS

ORIGINS AND CHEMISTRY

Statins, also known as 3-hydroxy-3methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, are the most commonly prescribed medications for hyperlipidemia. The lipid lowering benefit of statin drugs was discovered in 1976, and these agents were subsequently introduced in the 1980's.[92] The earlier statins were fungal metabolites but are now produced synthetically. Currently six statins are available in the U.S. Of these, lovastatin (Mevacor® by Merck) and pravastatin (Pravachol® by Bristol-Myers Squibb) are natural products derived from fungal metabolites. Simvastatin (Zocor® by Merck) is a semi-synthetic derivative. Fluvastatin (Lescol® by Novartis) was the first entirely synthetic compound, followed by a generation of other synthetic statins such as atorvastatin (Lipitor® by Pfizer) and most recently rosuvastatin (Crestor® by AstraZeneca). Cerivastatin (Baycol® by Bayer) is also a synthetic statin, but was withdrawn from the market in 2001 due to occurrence of fatal rhabdomyolysis.

MECHANISM OF ACTION

Statins work by suppressing the biosynthesis of cholesterol. Figure 1.1 illustrates the biosynthetic pathway of cholesterol.

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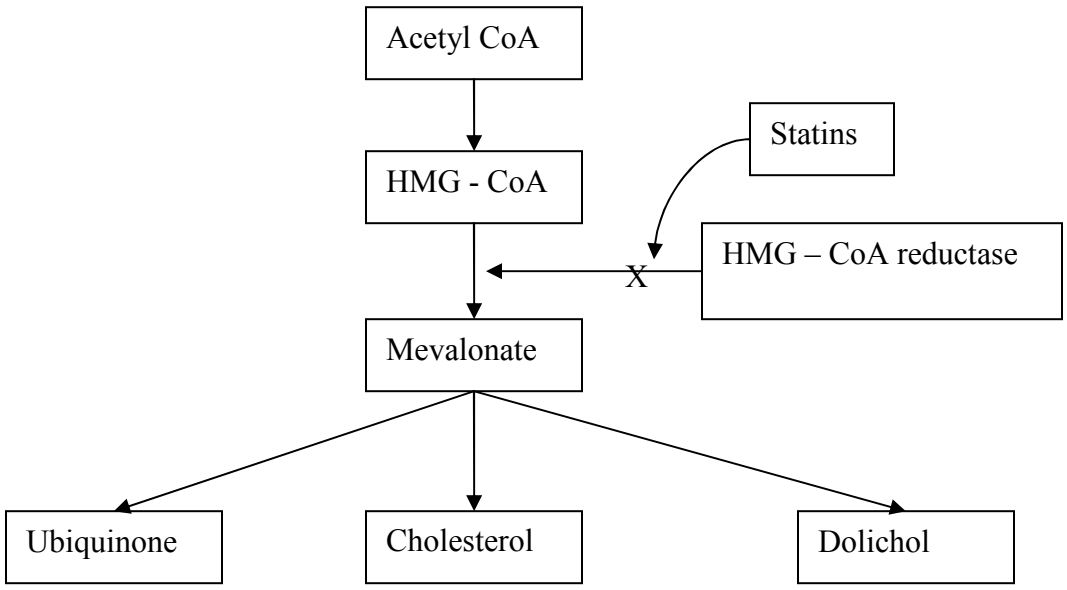
[92] Gaw A. *The discovery and development of the statins*. In: Gaw A, Packard C J, Shepherd. J, eds. Statins : the HMG-CoA reductase inhibitors in perspective. London, New York: Martin Dunitz ; Independence, KY, 2004:24-28.

Figure 1.1: The cholesterol biosynthetic pathway, showing the rate limiting step catalyzed by HMG-CoA reductase



Source: Evans M, Rees A. Effects of HMG-CoA reductase on skeletal muscle: are all statins the same? *Drug Saf* 2002;25:649-663.

The rate limiting enzyme in this pathway is 3-hydroxy-3-methylglutaryl coenzyme reductase A (HMG-CoA), which catalyzes the conversion of HMG-CoA to mevalonate.[93] Statin competitively inhibit the enzyme HMG-CoA reductase, which decreases the cholesterol synthesis by some 10 to 60%, depending on the dose and individual statin.[94] This decrease in cholesterol biosynthesis results in an increase in the number of LDL receptors in the liver and consequently, increased clearance of LDL from

[93] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* 2005;19:117-25.
[94] Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002;41:343-70.

plasma. LDL levels are also decreased due to decreased hepatic production of VLDL and increased breakdown of VLDL.[95] Along with cholesterol, the synthesis of ubiquinone and dolichol is also affected, which may lead to toxicity of statins.

PHARMACOKINETICS OF STATINS

Lovastatin and simvastatin are administered as lactone pro-drugs, and are enzymatically hydrolyzed in vivo to their active, hydroxyl-acid form. All the other statins are administered as the active hydroxyl acid.[96] Table 1.2 summarizes some of the key pharmacokinetic properties of the individual statins.

[95] Slater EE, MacDonald JS. Mechanism of action and biological profile of HMG CoA reductase inhibitors. A new therapeutic alternative. *Drugs* 1988;36 Suppl 3:72-82.
[96] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* 2005;19:117-25.

Table 1.2: Comparison of statin drugs on pharmacokinetic parameters including bioavailability, solubility, protein binding, elimination half-life, presence of active metabolites, and isoenzymes used for metabolism

Pharmacokinetic Parameter	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Atorvastatin	Cerivastatin[a]	Rosuvastatin
Bioavailability (%)	5	18	5	24	12	60	20
Solubility	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic
Protein binding	>95	~50	95-98	>98	98	>99	90
Active metabolites	Yes	No	Yes	No	Yes	Yes	Minor
Elimination half-life (h)	3	1.8	2	1.2	14	2.5	19
Isoenzyme[b]	3A4	None	3A4	2C9	3A4	3A4, 2C8	2C9/2C19

Source: Schachter M. Chemical, pharmacokinetic, and pharmacodynamic properties of statins: an update. F*undam Clin Pharmacol* 2005;19:117-125

[a] Voluntarily withdrawn from clinical use

[b] Isoenzyme refers to the specific isoenzyme in the cytochrome P450 system that is responsible for the metabolism of each drug.

As seen in Table 1.2, statins generally possess a low systemic bioavailability (except cerivastatin) indicating extensive first-pass extraction. Also, all statins are extensively bound to plasma proteins, with the exception of pravastatin, resulting in low systemic exposure to the active drug.[97]

The two important pharmacokinetic properties that differ across statins are the solubility of statins and the metabolism of statins by isoenzymes. These properties affect drug-drug interactions, and toxicity of statins.[98] Lipophilic statins can enter the hepatocyte cell membrane through passive diffusion and inhibit cholesterol synthesis. However, these statins will also pass through other cell membranes and can lead to statin toxicity. In contrast, hydrophilic statins have carrier-mediated uptake in the liver, making them hepatoselective and less toxic.[99]

Statins that are lipophilic must be metabolized to a water soluble form for renal excretion. This process depends on cytochrome P450 (CYP450) isoenzymes.[100] The CYP450 isoenzyme metabolizes a large number of drug products in humans. As a result, a lipophilic statin is subject to metabolic inhibition by concomitantly administered drugs with stronger affinity for the same isoenzyme.[101] It has now been recognized that statins metabolized by CYP450 system are more likely to produce muscle toxicity because of drug interactions with other drugs that are metabolized by the same isoenzyme system;

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[97] Ibid.
[98] Bottorf M. Safety and statins: Pharmacologic and clinical perspective. *Am J Manag Care* 2004;4:S30-S37.
[99] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* 2005;19:117-25.
[100] Bottorf M. Safety and statins: Pharmacologic and clinical perspective. *Am J Manag Care* 2004;4:S30-S37.
[101] Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002;41:343-70.

drug interactions increase levels of statins in the blood with an increased risk of toxicity.[102] In contrast, a water soluble statin depends very little, if at all, on the CYP450 system, making it less susceptible to drug interactions.

In summary, the pharmacokinetic properties differ across statins, especially in terms of their dependence of CYP450 system. It is important to understand these subtle differences between statins, as they may have clinical consequences.

EFFICACY OF STATINS

Statins are the most commonly prescribed drugs for the treatment of hyperlipidemia because of their efficacy in reducing LDL levels. In a recent general review of statin drugs, Maron et al.[103] compared the efficacy of different doses of the statins available in patients without hypertriglyceridemia. Their findings are shown below in Table 1.3.

[102] Muscari A, Puddu GM, Puddu P. Lipid-lowering drugs: are adverse effects predictable and reversible? *Cardiology* 2002;97:115-21.
[103] Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000;101:207-13.

Table 1.3: Comparison of different doses of statin drugs on the efficacy of decreasing total cholesterol, LDL, triglycerides, and increasing HDL levels[a]

Statin Drug and Dose (mg)						Percent Change in Lipid and Lipoprotein Levels			
Atorvastatin	Simvastatin	Lovastatin	Pravastatin	Fluvastatin	Cerivastatin	Total cholesterol decrease	LDL decrease	HDL increase	Triglyceride decrease
-	10	20	20	40	0.2	-22%	-27%	4-8%	-10-15%
10	20	40	40	80	0.4	-27%	-34%	4-8%	-10-20%
20	40	80	-	-	-	-32%	-41%	4-8%	-15-25%
40	80	-	-	-	-	-37%	-48%	4-8%	-20-30%
80	-	-	-	-	-	-42%	-55%	4-8%	-25-35%

Source: Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000;101:207-213.
[a] Rosuvastatin was not available in the market at the time of this review

As seen from Table 1.3, the dose required to lower LDL levels by a specific amount varies substantially among the statins. For example, to lower LDL levels by 41% requires 40 mg of simavstatin but 80 mg of lovastatin. In addition, the dose-response relationship for all statins is curvilinear; doubling the dose above the minimal effective dose only decreases the LDL levels by an additional six percent. The maximum reduction in LDL levels ranges from 24% to 60%.[104] In summary, statins are effective in reducing lipid levels, though their effectiveness varies by type and dose of statin. Many clinical trials have been conducted to evaluate the efficacy of statins.

Clinical trials of statins

The clinical benefits of statins have been demonstrated in data from seven major randomized controlled trials (RCT's), including nearly 57,000 patients. Of these seven trials, three trials (the Scandinavian Simvastatin Survival Study [4S],[105] the Cholesterol and Recurrent Events Trials [CARE],[106] and the Long-Term Intervention with Pravastatin in Ischemic Disease [LIPID] trial[107]) were secondary prevention trials, and two trials (the West of Scotland Coronary Prevention Study [WOSCOPS][108] and the Air Force/ Texas

[104] Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999;341:498-511.
[105] The Scandinavian Simvastatin Survival Study (4S) Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet* 1994;344:1383-9.
[106] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.
[107] The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.
[108] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301-7.

Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS][109]) were primary prevention trials. A summary of trials for the secondary and primary prevention was published by Maron and colleagues.[110] The results of this summary can be found in Table 1.4.

[109] Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-22.

[110] Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000;101:207-13.

Table 1.4: Summary of secondary and primary prevention trials of the effect of statins on reduction of LDL, mortality, and CHD events as published by Maron and colleagues

Study	Intervention	n (%women)	% LDL Reduction	% Reduction in Mortality	% Reduction in CHD events
Secondary Prevention Trials					
4S[a]	Simvastatin 20-40 mg/d	4444 (19)	35	30	34
CARE[b]	Pravastatin 40 mg/d	4159 (14)	32	9[f]	24
LIPID[c]	Pravastatin 40 mg/d	9014 (17)	25	22	24
Primary Prevention Trials					
WOSCOPS[d]	Pravastatin 40mg/d	6595 (0)	26	22	31
AFCAPS/TexCAPS[e]	Lovastatin 20-40 mg/d	6605 (15)	25	0[f]	37

Source: Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000;101:207-213

[a.] The Scandinavian Simvastatin Survival Study (4S) Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet* 1994;344:1383-9.

[b.] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.

[c.] The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.

[d.] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301-7.

[e.] Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-22.

[f.] p value not significant

Among the secondary prevention trials, the 4S trial demonstrated a reduction in coronary events in both men and women, in individuals younger and older than 60 years of age, and in subjects with risk factors such as smoking, hypertension, and diabetes.[111] The CARE study extended the results of 4S to individuals with average cholesterol levels. In this study, patients with LDL levels below 125 mg/dL showed no reduction in coronary events, suggesting that statin treatment of CHD patients with low LDL levels may not be warranted.[112] The LIPID study extended the findings of CARE by including subjects with unstable angina and by using CHD death as primary end point. There was a 24% reduction in CHD deaths in the pravastatin group.[113]

In the area of primary prevention, the WOSCOPS trial showed significant risk reductions in nonfatal myocardial infarction and coronary deaths after five years.[114] In AFCAPS/TexCAPS study, lovastatin reduced the risk for a first acute major coronary event, in men and women with average LDL levels and low HDL levels.[115]

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[111] Pyorala K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997;20:614-20.

[112] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.

[113] The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.

[114] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301-7.

[115] Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-22.

Apart from these five trials, data from two additional RCT's (the Heart Protection Study [HPS][116] and the Lescol Intervention Prevention Study [LIPS][117]) have been reported. The HPS trial, which is the largest study to date, showed the benefits of statin therapy (simvastatin) in both primary and secondary prevention patients who are at high risk of cardiovascular events. Results showed a reduction in cholesterol levels, CHD events and total mortality, and benefits were seen in sub-populations including women, people older than 70 years, and individuals with LDL levels less than 116 mg/dL.[118]

The LIPS trial assessed the effects of fluvastatin in patients who successfully completed their first percutaneous coronary intervention. Results showed a 22% reduction in major adverse coronary events. These benefits were more pronounced in patients with diabetes and those with multivessel disease.[119]

All of these trials, demonstrate the beneficial effect of statins in the reduction of LDL levels, and CHD associated mortality and morbidity. These benefits have been observed irrespective of the age group, cholesterol levels, various CHD risk factors, and in the presence or absence of prior CHD.

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[116] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.

[117] Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;287:3215-22.

[118] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.

[119] Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;287:3215-22.

SAFETY OF STATINS

Statins are generally well-tolerated. The most common side effects are headaches and gastrointestinal upset (e.g., constipation, flatulence, dyspepsia, and abdominal pain). Rare cases of peripheral neuropathy and polyneuropathy have been reported, but a clear association with statin use has not been demonstrated.[120,121] Discontinuations due to statin-related side-effects are generally in the range of one to five percent, and are not different compared to patients taking placebo.[122] The most serious adverse effects related to statin use include an elevation of liver enzymes and myopathy. Severe rhabdomyolysis resulting in deaths was the reason of withdrawal of cerviastatin from the market. A discussion of both the serious side-effects follows.

Statins and hepatotoxicity

Statins are highly hepatospecific and therefore appear to inhibit cholesterol synthesis in the liver greater than any other tissue.[123] Elevated hepatic transaminases are observed in about 0.5 to 2.0 percent of statin recipients and are usually dose-dependent.[124] It is not yet known, however, whether these elevations with statin therapy constitute true hepatotoxicity. Hepatic transaminase elevations are reversible with a reduction of dose and usually do not reappear. Elevations in liver enzymes are not

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[120] Backes JM, Howard PA. Association of HMG-CoA reductase inhibitors with neuropathy. *Ann Pharmacother* 2003;37:274-78.
[121] Gaist D, Garcia Rodriguez LA, Huerta C, et al. Are users of lipid-lowering drugs at increased risk of peripheral neuropathy? *Eur J Clin Pharmacol* 2001;56:931-3.
[122] Blum CB. Comparison of properties of four inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. *Am J Cardiol* 1994;73:3D-11D.
[123] Gotto AM, Jr. Safety and statin therapy: reconsidering the risks and benefits. *Arch Intern Med* 2003;163:657-9.
[124] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

unique to statins and have been observed with other classes of lipid lowering agents. This suggests that the increase may be due to changes in lipid metabolism induced by these drugs and not by drugs themselves.[125]

Progression to liver failure specifically due to statins is very rare. Nevertheless, statins have been associated with rare cases of hepatocellular toxicity and jaundice.[126,127] As result, patients with significant liver disease, heavy alcohol consumption, or chronic hepatitis should not receive statins.

The most clinically significant adverse reaction of statin therapy to date is myopathy and its progression to life-threatening rhabdomyolysis. Muscle-related events and myopathy associated with statins are the focus of this dissertation and are described in detail in the next section.

[125] Gotto AM, Jr. Safety and statin therapy: reconsidering the risks and benefits. *Arch Intern Med* 2003;163:657-9.
[126] Ibid.
[127] Hartleb M, Rymarczyk G, Januszewski K. Acute cholestatic hepatitis associated with pravastatin. *Am J Gastroenterol* 1999;94:1388-90.

SECTION III

MYOPATHY

Myopathy is the most serious adverse effect associated with the statins. Although, the incidence of clinically important myopathy is low, the risk may increase in presence of many factors. This section describes the various types of myopathy, its mechanism, risk factors for myopathy, and evidence from clinical trials and clinical practice settings.

MYOPATHY: DEFINITION, SUBDIVISION AND CLASSIFICATION

The literature to describe muscle toxicity or myopathy associated with statins is not consistent, due to the lack of clear definitions. Recently, the American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute (ACC/AHA/NHBLI) clinical advisory on the use and safety of statins classified muscle toxicity into four classes.[128] These are as follows:

- Myopathy – It is a general term referring to any disease of the muscles; myopathies can be acquired or inherited and can occur at birth or later in life.
- Myalgia – It is defined as muscle aches or weakness without any elevation in creatine kinase (CK) levels. Myalgia is the most common of the myotoxic effects of statins.

[128] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

- Myositis – It is defined as muscle symptoms with increased CK levels. It is characterized by muscle weakness and is usually self-limiting.
- Rhabdomyolysis – It is defined as muscle symptoms with an increase in CK levels greater than 10 times the upper limit of normal (ULN), and an elevated creatinine usually with brown urine and urinary myoglobin.

Besdies statins some of the drugs that have been associated with myopathy include corticosteroids, antimalarials, colchicine, penicillamine, zidovudine, and drugs associated with abuse, such as alcohol and cocaine.[129] The extent of muscle toxicitiy depends on many factors, and more than one mechanism of action has been proposed for the muscle damage.

MECHANISM OF ACTION

There is little information on the mechanism by which statins cause myopathy. However, several theories have been proposed based on the biosynthetic pathways which were presented earlier in Figure 1.1.

One theory suggests that inhibiting cholesterol synthesis reduces the cholesterol content of skeletal muscle cell membranes. Alteration of skeletal muscle cell membrane content can lead to changes in the electrical properties of the membrane and instability of the cell membrane permeability of the myocyte.[130,131] This may be responsible for the observed statin-associated myopathy.

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[129] Krikorian S. Drug-induced myopathies. *US Pharmacist* 1999;24:33-34.
[130] Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004;116:408-16.
[131] Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001;35:1096-107.

Another theory suggests that reduced levels of ubiquinone are responsible for muscle injury.[132] Statins work by inhibiting the HMG-CoA reductase enzyme which is essential in the production of mevalonate (Figure 1.1). Mevalonate is also a precursor for ubiquinone, also known as coenzyme Q10 (CoQ10). Interruption in the synthesis of CoQ10 can lead to adverse effects of muscles. CoQ10 is a steroid isoprenoid enzyme that helps in formation of adenosine triphosphate (ATP) through oxidation of nutrients within cells.[133] CoQ10 serves as a powerful antioxidant and membrane stabilizer that is used by mitochondria for electron transport during oxidative phosphorylation. CoQ10 plays an important role in the functioning of skeletal and cardiac muscles. Inhibition of CoQ10 synthesis by statins causes intracellular ubiquinone deficiency. Futhermore, CoQ10 is transported in LDL particles. Statins lower LDL levels, which further reduces ubiquinone levels. As a result of this reduction in the CoQ10 levels, there is a decrease in the oxidative phosphorylation, which is needed for normal cellular respiration. This causes instability of muscle cell membrane resulting in myopathy.[134,135] A number of observations suggest that statin associated myopathy may be caused by CoQ10 deficiency. Mitochondrial dysfunction has been demonstrated in biopsy studies of patients treated with statins who experienced muscle symptoms.[136] Similarly case reports of patients with myopathy who improved clinically after administration of CoQ10

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[132] Jamal SM, Eisenberg MJ, Christopoulos S. Rhabdomyolysis associated with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am Heart J* 2004;147:956-65.
[133] Ibid.
[134] Ibid.
[135] Owczarek J, Jasinska M, Orszulak-Michalak D. Drug-induced myopathies. An overview of the possible mechanisms. *Pharmacol Rep* 2005;57:23-34.
[136] Phillips PS, Haas RH, Bannykh S, et al. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002;137:581-5.

supplementation have been reported.[137,138] However, no clinical study has yet provided support for this hypothesis.

Yet another theory suggests that mevalonate production in the biosynthetic pathway of cholesterol leads to activation of regulatory proteins such as guanosine triphosphate (GTP)-binding proteins.[139] These GTP-binding proteins are important in apoptosis or controlled cell death, which is a critical mechanism designed to assist in the remodeling and maintenance of tissue structure.[140] Inhibition of mevalonate production by statins leads to inappropriate activation of these proteins. As a result of inappropriate activation, apoptosis can cause pathological conditions. It has been suggested that statin-induced reductase inhibition triggers skeletal myocyte apoptosis and myopathy development.[141,142,143] Also, a dose-dependent increase in apoptosis due to statin therapy has been observed in vascular smooth muscle cells. Thus, it is possible that that same mechanism is involved in the inhibition of vascular smooth muscle cell's proliferation and apoptic cell death in muscle fibers.[144]

These are the theories that have been proposed for the mode of action statin-induced myopathies. Each of these theories continues to be investigated and additional

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[137] Chariot P, Abadia R, Agnus D, et al. Simvastatin-induced rhabdomyolysis followed by a MELAS syndrome. *Am J Med* 1993;94:109-10.
[138] Walravens PA, Greene C, Frerman FE. Lovastatin, isoprenes, and myopathy. *Lancet* 1989;2:1097-8.
[139] Tomlinson SS, Mangione KK. Potential adverse effects of statins on muscle. *Phys Ther* 2005;85:459-65.
[140] Ibid.
[141] Jamal SM, Eisenberg MJ, Christopoulos S. Rhabdomyolysis associated with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am Heart J* 2004;147:956-65.
[142] Owczarek J, Jasinska M, Orszulak-Michalak D. Drug-induced myopathies. An overview of the possible mechanisms. *Pharmacol Rep* 2005;57:23-34.
[143] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681-90.
[144] Owczarek J, Jasinska M, Orszulak-Michalak D. Drug-induced myopathies. An overview of the possible mechanisms. *Pharmacol Rep* 2005;57:23-34.

work is required to support these theories. Also it is possible that new theories may also evolve explaining the mechanism of myopathy due to statins.

MYOPATHY IN RANDOMIZED CONTROLLED TRIALS OF STATIN THERAPY

Clinical trials that have assessed the safety and efficacy of statins support a low incidence of serious muscle problems with statin therapy. Table 1.5 provides information on the rates of myopathy reported in seven clinical trials.[145]

[145] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681-90.

Table 1.5: Percent of patients with myalgia, and number of patients with myositis and rhabdomyolysis in different clinical trials of statin therapy as published by Thompson and colleagues

Drug	Study	No. of patients		% with myalgia		No. with myositis[a]		No. with rhabdomyolysis	
		Statin	Control	Statin	Control	Statin	Control	Statin	Control
Lovastatin	AFCAPS/TexCAPS[b]	3304	3301	NA	NA	21	21	1	2
Pravastatin	CARE[c]	2078	2081	NA	NA	0	4	0	0
	WOSCOPS[d]	3302	3293	3.5	3.7	NA	NA	0	0
	LIPID[e]	4512	4502	NA	NA	8	10	0	0
Simvastatin	4S[f]	2221	2223	NA	NA	6	1	1	0
	HPS[g]	10,269	10,267	32.9	33.2	11	6	5	3
Fluvastatin	LCAS[h]	214	215	NA	NA	1	2	0	0
Atorvastatin	MIRACL[i]	1538	1548	NA	NA	0	0	0	0
Cerivastatin	ENCORE[j]	114	119	NA	NA	2	0	NA	NA
Rosuvastatin[k]		12,400	0	3.1	NA	2	NA	1	NA

Source: Thompson PD, Clarkson P, Karas RH. Statin-induced myopathy. *JAMA* 2003;289:1681-1690
NA-Not available

[a.] Myositis was defined as a CK elevation of greater than 10 times the upper limit of normal

[b]. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;279:1615-22.

[c.] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-9.

[d]. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301-7.

[e.] The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.

Table 1.5: Percent of patients with myalgia, and number of patients with myositis and rhabdomyolysis in different clinical trials of statin therapy as published by Thompson and colleagues (Continued)

[f.] The Scandinavian Simvastatin Survival Study (4S) Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet* 1994;344:1383-9.

[g.] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.

[h.] Herd JA, Ballantyne CM, Farmer JA, et al. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *Am J Cardiol* 1997;80:278-86.

[i.] Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711-8.

[j.] Effect of nifedipine and cerivastatin on coronary endothelial function in patients with coronary artery disease: the ENCORE I Study (Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function). *Circulation* 2003;107:422-8.

[k.] Shepherd J, Hunninghake DB, Stein EA, et al. Safety of rosuvastatin. *Am J Cardiol* 2004;94:882-8.

As seen from Table 1.5, myopathy was not reported frequently during clinical trials, and there were few differences in the myopathy rates between the statin group and the control group. The first generation statins (lovastatin, pravastatin, and simvastatin) have been well evaluated for their safety and efficacy in large clinical trials (Table 1.5). In the prospective pravastatin pooling project,[146] which analyzed over 112,000 patient-years of pravastatin exposure, three subjects had high creatine kinase concentrations and there were no cases of rhabdomyolysis. In the 4S trial,[147] there were six cases of mild myositis and one case of rhabdomyolysis. In HPS trial,[148] one of the largest statin trials to date (20,536 patients), 32.9% of the simvastatin and 33.2% of the placebo participants complained of muscle symptoms. Rhabdodmyolysis occurred in five patients in the statin group and in the three placebo group patients. Similarly, for trials of lovastatin, there was no difference in the myopathy rates between the statin and the control group.

As compared to first generation statins, there are fewer clinical trials for second generation statins (fluvastatin, atorvastatin, cerivastatin, and rosuvastatin).[149] Fluvastatin and atorvastatin have demonstrated safety profiles similar to other statins in small studies (Table 1.5).[150] Rosuvastatin is a much newer drug and the safety profile of this drug will have to be monitored. Cerivastatin had similar safety profiles in clinical trials; however,

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[146] Pfeffer MA, Keech A, Sacks FM, et al. Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. *Circulation* 2002;105:2341-6.
[147] The Scandinavian Simvastatin Survival Study (4S) Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet* 1994;344:1383-9.
[148] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
[149] Jamal SM, Eisenberg MJ, Christopoulos S. Rhabdomyolysis associated with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am Heart J* 2004;147:956-65.
[150] Ibid.

it was later withdrawn from the market due to high risk of rhabdomyolysis (discussed later).

In summary, the incidences of myopathy, mild or severe, reported in clinical trials are between 0.1 percent and 5.0 percent, depending on dose and type of statin. However, many patients excluded from the trials receive these agents in clinical practice. Also, patients in clinical trials are generally better informed, and monitored very closely as compared to those in a "real-world" setting.[151,152] Therefore, these incidences may be underestimated in clinical trials compared to actual rates of myopathy in "real-world" situations.[153,154,155] The case of cerivastatin is an example where the incidence was low in clinical trials but the drug was later withdrawn from market due to increased rates of rhabdomyolysis. The next part looks at the life-cycle of cerivastatin from its marketing approval to its withdrawal.

CERIVASTATIN: MARKETING APPROVAL TO WITHDRAWAL

Cerivastatin was developed as a highly potent lipophilic, pure enantiomeric agent and has been evaluated in studies since 1993.[156] Cerivastatin is metabolized dually by two different isoenzymes in cytochrome P450 system (CYP 3A4 & CYP 2C9), and this

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[151] Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003;163:553-64.
[152] Jamal SM, Eisenberg MJ, Christopoulos S. Rhabdomyolysis associated with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am Heart J* 2004;147:956-65.
[153] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681-90.
[154] Jamal SM, Eisenberg MJ, Christopoulos S. Rhabdomyolysis associated with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am Heart J* 2004;147:956-65.
[155] Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003;163:553-64.
[156] Stein E. Cerivastatin in primary hyperlipidemia: a multicenter analysis of efficacy and safety. *Am J Cardiol* 1998;82:40J-46J.

dual mechanism was thought to improve its safety profile compared to other statins.[157] Based on the safety profile, the drug was marketed in 1998. At the initial approved doses of 0.2 and 0.3 mg, cerivastatin reduced LDL levels lower than the other statins available at the time. To achieve comparable levels of cholesterol lowering, new drug applications were made for 0.4 mg and 0.8 mg, which were approved subsequently in 1999 and 2000.[158] Premarketing clinical trials of cerivastatin up to doses of 0.4 mg, showed no risk of rhabdomyolysis. However, there was a significant increase in adverse events including myotoxicity in doses higher than 0.4 mg.[159] This was evident in the reports of post-marketing surveillance, which subsequently led to its withdrawal.

Psaty and colleagues[160] reviewed unpublished manufacturer's data on cerivastatin made available to public during lawsuit trials. The authors reported that the company had received seven case reports of rhabdomyolysis within 100 days of marketing the drug. However, the company did not report this safety data to FDA. Five of the seven cases had used gemfibrozil concomitantly with cerivastatin. These reports continued to increase over time. As a result, the FDA issued a specific contraindication of the use of cerivastatin and gemfibrozil. In spite of this label change, there was continued use of the two drugs together, and then higher dose (0.8 mg) of cerivastatin was introduced in the

[157] Evans M, Rees A. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Saf* 2002;25:649-63.
[158] Psaty BM, Furberg CD, Ray WA, et al. Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis. *JAMA* 2004;292:2622-2631.
[159] Ose L, Luurila O, Eriksson J, et al. Cerivastatin gender effect: sub-analyses of results from a multinational, randomised, double-blind study. Cerivastatin Study Group. *Curr Med Res Opin* 2000;16:80-7.
[160] Psaty BM, Furberg CD, Ray WA, et al. Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis. *JAMA* 2004;292:2622-2631.

market.[161,162] During this period, the incidence of rhabdomyolysis continued to increase, and 52 worldwide deaths were recorded with the use of cerivastatin.[163] After these reports, cerivastatin was withdrawn from the market. The US accounted for 31 of the 52 deaths, and 12 of the case fatalities involved a combination of cerivastatin and gemfibrozil. In the majority of the cases where cerivastatin was used alone and a death occurred, the dose was 0.8 mg.[164] Thus, severe myopathy appeared to occur at higher doses and in cases where patients took the drug with gemfibrozil.

The experience with cerivastatin emphasizes the need to continuously monitor adverse drug reactions after marketing of the drug, even though the drug has been proven safe in clinical trials. This is because, as mentioned before, clinical trial settings are different from "real-world" practice settings, and many factors come into play in the actual setting. Postmarketing surveillance is one way to monitor adverse reactions after marketing of the drug.

POSTMARKETING SURVEILLANCE: REPORTS OF MYOPATHY/ RHABDOMYOLYSIS TO THE FOOD AND DRUG ADMINISTRATION

Postmarketing surveillance of drug-related events is one method that plays a valuable role in early identification of adverse events associated with drug therapy.

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[161] Ibid.
[162] Evans M, Rees A. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Saf* 2002;25:649-63.
[163] Farmer JA. Learning from the cerivastatin experience. *Lancet* 2001;358:1383-5.
[164] Evans M, Rees A. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Saf* 2002;25:649-63.

Postmarketing surveillance begins when the drug enters the market. This monitoring of drug safety helps promote safe drug therapy, and therefore protects the health of public.

In the US, FDA is responsible for postmarketing surveillance. The Office of Drug Safety (ODS) of the FDA receives voluntary spontaneous reports of adverse drug reactions, primarily from physicians and pharmacists, and through drug companies, and rarely from consumers.[165] FDA's Adverse Event Reporting System (AERS) is a repository of reports of adverse drug reactions. This database can be used to identify drug-related events that occur in clinical practice.[166,167]

Case-reports of myopathy associated with statin use began to appear in the literature as early as 1988; some of them involved potentially interacting medications.[168] The FDA database has been reviewed multiple times, with varying time periods, to identify cases of statin-associated rhabdomyolysis. Omar and colleagues[169] reviewed the database first, and found 601 cases of statin-associated rhabdomyolysis from November 1997 through March 2000. Thompson et al.[170] reviewed the FDA database to identify cases of statin-associated rhabdomyolysis from January 1, 1990, through March 31, 2002. The authors found 3339 cases of statin-associated rhabdomyolysis. Chang et al.[171]

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[165] Adverse event reporting system. US Food and Drug Administration, 2005. Available at: http://www.fda.gov/cder/aers/default.htm. Accessed on: August 18

[166] Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001;35:1096-107.

[167] Chang JT, Staffa JA, Parks M, et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Saf* 2004;13:417-26.

[168] Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003;163:553-64.

[169] Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001;35:1096-107.

[170] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681-90.

[171] Chang JT, Staffa JA, Parks M, et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Saf* 2004;13:417-26.

reviewed the database from the initial date of marketing for each of the statins until July 2001, and extensively examined the cases of rhabdomyolysis and calculated the reporting rates for this event. Table 1.6 summarizes the results of this study. Table 1.7 illustrates the reporting rates for rhabdomyolysis.

Table 1.6: Mean age, gender, number of days to onset, mean dose, and outcomes of patients who had rhabdomyolysis associated with the use of different statin therapies from 1988 through July 2001 as published by Chang and colleagues

Selected Characteristics n = 866	Lovastatin n = 180	Pravastatin n = 19	Simvastatin n = 136	Fluvastatin n = 1	Atorvastatin n = 51	Cerivastatin n = 479
Approval Year	1987	1991	1991	1993	1996	1997
Mean Age (years)[a]	61	68	65	70	60	68
Sex[a]						
Female	92	13	53	0	17	256
Male	80	6	79	1	31	209
Number of days to onset[a]						
Minimum-Maximum	5-1825	2-1080	4-900	10	7-2190	2-412
Mean	241	234	51	10	309	68
Mean Dose (mg/day)[a]	50	25	51	-	29	0.5
Outcome[a,b]						
Hospitalized	147	17	118	1	43	426
Died	19	3	14	0	6	38
Non-serious	11	2	13	0	4	12
Unknown	22	0	5	0	4	41

Source: Chang JT, Staffa JA, Parks M, et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Saf* 2004; 13:417-426.

[a.] Data for all cases was not available. Due to incomplete data, means and number of cases for selected characteristics may be less than actual reported number.

[b.] More than one outcome is possible.

Table 1.7: Years analyzed, number of prescriptions dispensed, number of cases and crude reporting rates/100,000 prescriptions of rhabdomyolysis for different statin therapies as published by Chang and colleagues

	Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Atorvastatin	Cerivastatin
Years analyzed	1988-July 2001	1992-July 2001	1992-July 2001	1994-July 2001	1997-July 2001	1998-July 2001
# of Rx's (000's)[a]	99,485	83,673	120,188	38,119	149,706	11,172
Cases	180	19	136	1	51	479
Crude reporting rate/100,000 Rx	0.18	0.02	0.11	0.00	0.03	4.29

Source: Chang JT, Staffa JA, Parks M, et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Saf* 2004; 13:417-426.

[a.] All dispensed Rxs for all years the drug was marketed, excluding long term care (Source: IMS Health)

As seen from Table 1.6, a total of 866 cases of rhabdomyolysis were reported to the FDA from 1988 through July 2001. More than 80% of the cases for each of the statin drug product resulted in hospitalization. Also, the number of cases of rhabdomyolysis was much higher for cerivastatin as compared to any other statins. Of the 866 reported cases, 482 (56%) cases were associated with monotherapy and 384 (44%) cases were associated with combination therapy of statin and gemfibrozil.[172] In an earlier study by Omar and colleagues,[173] rhabdomyolysis was associated with a combination of statins and other drugs (including gemfibrozil) that interfere with the metabolism of statins (e.g. CYP 3A4 inhibitors). In addition to the statins mentioned in Table 1.6, rosuvastatin was marketed in October 2003. Alsheikh-Ali and colleagues[174] reviewed the FDA database for adverse events of rosuvastatin. Within one-year of marketing the drug, there were 145 reports of rosuvastatin-associated rhabdomyolysis. As compared with the other statins, over the concurrent time frame and during their first year of marketing, rosuvastatin was several-fold more likely to be associated with rhabdomyolysis.

As shown in Table 1.7, the reporting rates for rhabdomyolysis were similar and much lower than one per 100,000 prescriptions for all statins, except cerivastatin. The reporting rate for cerivastatin was 4.29/100,000 prescriptions but this rate was increased to 1249/100,000 prescriptions for a combination of cerivastatin and gemfibrozil. As discussed before, because of high rate of deaths due to cerivastatin-associated rhabdomyolysis, the drug was withdrawn from the market.

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[172] Ibid.
[173] Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001;35:1096-107.
[174] Alsheikh-Ali AA, Ambrose MS, Kuvin JT, et al. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. *Circulation* 2005;111:3051-57.

Although AERS is good source to monitor postmarketing rates of adverse events, it has many limitations. The data used in the studies above reflect adverse event reporting rates, and not actual adverse event rates.[175] Since AERS is a voluntary reporting system, it is left completely to the discretion of the health care professional whether or not to report an adverse event. Also, it is known that most adverse drug reactions are severely underreported.[176,177] Hence, the rates presented in Table 1.7 are likely underestimates of the true rate of the adverse events. Therefore, it is important to scientifically design studies that can give true estimates of the risk of myopathy. Epidemiologic studies are one method that can provide true estimates of statin-associated myopathy.

EPIDEMIOLOGICAL STUDIES OF MYOPATHY

The literature on epidemiologic studies of statin-associated myopathy is very sparse. This may be because myopathy is such a rare event that a large population is required to do the study. Four known studies have estimated the incidence of myopathy in patients using statins. Two of these studies were done on the population of United Kingdom using the General Practice Research Database (GPRD) database and two studies were done in the U.S. using large managed care databases.

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[175] Ibid.
[176] Chang JT, Staffa JA, Parks M, et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Saf* 2004;13:417-26.
[177] Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001;35:1096-107.

Gaist and colleagues[178] conducted a population-based cohort study to estimate the risk of myopathy associated with use of statins and fibrates. This was one of the earliest studies done estimating the incidence of myopathy. The authors utilized GPRD, which contains data from general practices in United Kingdom, to determine the risk of myopathy. Three cohorts of individuals, aged 40 to 74, were identified from 1991 to 1997. The first cohort consisted of persons using a lipid lowering drug; the second included those patients who had a diagnosis of hyperlipidemia but did not use a lipid-lowering drug; and the third cohort were persons from general population with no diagnosis of hyperlipidemia. The authors identified myopathy cases using Oxford Medical Information System (OXMIS) codes and then verified the cases using patient charts. The incidence rate of myopathy in the cohort of users of lipid-lowering drugs was 2.3 per 10,000 person years (95% CI: 1.2-4.4) which exceeded the incidence rates observed in the non-treated hyperlipidemia cohort [0 per 10,000 person years (95% CI: 0.0-0.4)] and the general population [0.2 per 10,000 years (95% CI: 0.1-0.4). The relative risks of myopathy in current users of fibrates and statins as compared to non-users were 42.4 (95% CI: 11.6-170.5) and 7.6 (95% CI: 1.4-41.3), respectively. The authors concluded that although the absolute risk of myopathy for statin and fibrate users is small, the relative risk of myopathy associated with lipid-lowering drugs is high, with fibrates having the greatest risk.

[178] Gaist D, Garcia Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565-9.

Black and Jick also analyzed the GPRD database to estimate the risk of rhabdomyolysis with lipid lowering agents. Among 2935 concurrent users of statin and fibrates, only one patient developed rhabdomyolysis.[179]

Recently, a very extensive study was conducted estimating the risk and risk factors of rhabdomyolysis in users of statins and fibrates, alone or as a combination therapy. Graham and colleagues[180] determined the incidence of hospitalized rhabdomyolysis using claims data from health care plans across the US. The average incidence for monotherapy with statins was 0.44 (95% CI: 0.20-0.84) per 10,000 years. This incidence rate increased for patients above 65 years of age and for patients with diabetes mellitus. Cerivastatin was not included in this analysis. The incidence for combined statin and fibrate users was 5.98 (95% CI: 0.72-216.0) per 10,000 patient-years. Statin-fibrate combination users had 12-fold increase in risk of myopathy as compared to statin users only (RR: 12.2; 95% CI: 2.59–57.44). This risk was further increased in patients 65 years and older with diabetes mellitus (RR: 48; 95% CI: 5.2-446.0). The authors concluded that the risk of rhabdomyolysis was low for statin monotherapy. However, the risk increased in patients using combination therapy and patients with certain risk factors.

A more recent study used administrative claims database from diverse regions in US to evaluate the incidences of hospitalizations related to adverse effects including myopathy for lipid lowering agents. Incidence of hospitalizations for myopathy in

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[179] Black C, Jick H. Etiology and frequency of rhabdomyolysis. *Pharmacotherapy* 2002;22:1524-26.
[180] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.

patients treated only with statins varied from 1.58 for fluvastatin to 3.84 for pravastatin per 10,000 person-years. Risk of hospitalizations due to myopathy increased in presence of hypertension (RR: 5.13; 95% CI: 2.4 –10.85) and if patients received potentially interacting medications concurrently with statins (RR: 6.01; 95% CI: 2.08–17.38).[181] The authors concluded that statin monotherapy is well-tolerated; however, the risk of myopathy increases in presence of PIMs.

Only one study has estimated the prevalence of myopathy in patients using statins alone or in combination with potentially interacting medications.[182] This study estimated the prevalence of myopathy to be 0.12% in statin alone users and 0.22% in statins and potentially interacting medication users. This difference in prevalence was statistically significant ($p = 0.05$).[183] Most of the myopathy events were related to an increase in statin dose or addition of potentially interacting medication.

In summary all of these studies demonstrate that the risk of myopathy (mostly rhabdomyolysis) is low with statin monotherapy. However, this risk may increase in presence of fibrates or other potentially interacting medications and patients with certain characteristics. Presence of risk factors can greatly affect the risk of myopathy in patients. The next section describes the risk factors of myopathy.

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[181] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[182] Shanahan RL, Kerzee JA, Sandhoff BG, et al. Low myopathy rates associated with statins as monotherapy or combination therapy with interacting drugs in a group model health maintenance organization. *Pharmacotherapy* 2005;25:345-51.
[183] Ibid.

RISK FACTORS FOR MYOPATHY

The risk factors for myopathy can be divided into four main factors: demographic factors, health-related factors, treatment factors and physician-related factors. The next part describes each of the factors that affect myopathy.

Demographic factors

Three demographic factors that may affect the risk of myopathy are age, gender, and ethnicity/race.

Age

Age is one of the risk factors for myopathy.[184] The risk of myopathy increases with age due to the effect of aging on muscles.[185] In two studies that estimated the risk of myopathy in statin users (mentioned above), people above the age of 65 had a higher risk of myopathy than younger patients.[186,187] Therefore, increasing age is an important risk factor of myopathy.

Gender

Females have a higher risk of myopathy than males.[188] This is based on evidence from case reports and spontaneous reporting systems. However, in the two previous

[184] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[185] Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004;116:408-16.
[186] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[187] Gaist D, Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565-9.
[188] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

studies done, there was no difference in the relative risk of myopathy based on gender. More research is needed to determine the effect of gender on the risk of myopathy.

Ethnicity/race

Ethnicity/race could have an impact on the risk of myopathy. Most clinical trials did not incorporate different ethnicities/races to examine their safety profile in this population. It is not very clear whether ethnicity/race has an impact of the risk of myopathy. However, rosuvastatin pharmacokinetic studies show that there is a greater risk of myopathy in Asians than in other sub-populations.[189] The difference in genetic makeup across ethnicities/races may play an important role in the risk of myopathy among patients.

Health risk factors

There are two main health risk factors: lifestyle factors and co-morbidity factors. These factors are known to increase the risk of myopathy. Each of these factors is described in detail below.

Lifestyle factors:

Physical activity

Patients treated with statins may experience an increase in plasma creatine kinase (CK) levels following exercise. This may be associated with disruption of muscle cell membrane.[190] Among 14 men taking lovastatin, CK levels were increased in two, 24

[189] Crestor, [package insert]. Wlimington, Del: AstraZeneca Pharmaceuticals; 2005;
[190] Ucar M, Mjorndal T, Dahlqvist R. HMG-CoA reductase inhibitors and myotoxicity. *Drug Saf* 2000;22:441-57.

hours after exercise.[191] This increase in CK levels may result in increased risk of myopathy.

Body size

Small body size increases the risk of myopathy.[192] This is related to volume of distribution of drug in thin or frail people.[193] As a result, higher concentrations of drug may be present in the body increasing the risk of myopathy.

Increased consumption of grapefruit juice

Large quantities of grapefruit juice (usually more than 1 quart per day) greatly increase the risk of myopathy.[194] Grapefruit inhibits an important enzyme (CYP450) in the metabolism of statins which increases the concentration of statins in the blood and thereby increases the risk of myopathy.[195]

Alcohol abuse

Excessive alcohol intake independently predisposes a patient to the risk myopathy.[196] Statin use in such patients increases the risk of myopathy in these patients.

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[191] Thompson PD, Gadaleta PA, Yurgalevitch S, et al. Effects of exercise and lovastatin on serum creatine kinase activity. *Metabolism* 1991;40:1333-6.
[192] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[193] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681-90.
[194] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[195] Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs* 2004;4:281-97.
[196] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

Co-morbidity factors:

Diabetes

Diabetes is considered as a risk factor for myopathy. This is based on case reports where many of the patients reporting myopathy/rhabdomyolysis had diabetes. Graham et al.[197] reported that the risk of rhabdomyolysis increased in patients with diabetes on statin monotherapy as well as on statin-fibrate combination. It has been postulated that patients with diabetes have reduced drug metabolism which increases the concentration of statins in blood thereby increasing the risk of myopathy.[198]

Renal insufficiency

In patients with renal insufficiency the risk of myopathy is higher independent of statin use. This is due to altered drug metabolism and polypharmacy in these patients.[199] In presence of statin use, the risk increases further.

Hepatic dysfunction

NCEP guidelines recommend preventing use of statins in patients with active or chronic liver diseases.[200] Such diseases increase the risk of hepatotoxicity. Presence of these diseases can also inhibit the metabolism of statins as liver is the primary path of metabolism. This can lead to increase in statin blood levels and risk of myopathy.

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[197] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[198] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681-90.
[199] Sica DA, Gehr TW. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and rhabdomyolysis: considerations in the renal failure patient. *Curr Opin Nephrol Hypertens* 2002;11:123-33.
[200] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.

Hypothyroidism

Hypothyroidism predisposes patients to myopathy independent of statin use. Clinical manifestations of hypothyroidism include proximal muscle weakness and elevation of creatine kinase levels.[201] Such manifestations are increased when these patients use statins.

Treatment-related factors

There are two main treatment-related factors: type and dose of statin, and receipt of potentially interacting medications with statins.

Type and dose of statin

The type and dose of statin used may contribute to the risk of myopathy. Factors that increase the concentration of statins in the blood enhance the risk of myopathy. According to the ACC/AHA/NHLBI clinical advisory on statins, myopathy is more likely to occur at higher statin doses than lower doses.[202] This is because the higher the dose, the greater the concentration of statin in blood and greater the risk of myopathy.

In addition to the dose, the type of statin used can also affect the risk of myopathy. As discussed, the pharmacokinetic properties of statins differ and this affects the risk of myopathy (Table 1.2). The first metabolic property that differs across statins is the solubility of statins. Lipophilic statins penetrate into the peripheral tissue more

[201] Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004;116:408-16.
[202] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

readily than hydrophilic statins, and therefore are more likely to produce the muscular effects.[203]

The second metabolic property that differs across statins is the method of metabolism of statins. The statins are metabolized mainly by CYP450 system, except pravastatin. This cytochrome system is also responsible for the metabolism and elimination of many other pharmacologic agents. This results in drug interactions with statins and may increase the concentration of statins in the blood which may lead to myopathy.[204,205]

Statins and potentially interacting medications is the focus of this dissertation and is discussed in detail in the next section.

[203] Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004;116:408-16.
[204] Bottorf M. Safety and statins: Pharmacologic and clinical perspective. *Am J Manag Care* 2004;4:S30-S37.
[205] Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002;41:343-70.

SECTION IV

STATINS AND POTENTIALLY INTERACTING MEDICATIONS

Myopathy is more likely to occur when statin drugs are administered with certain potentially interacting medications. Drugs that interact with statins either increase the concentrations of statins in the blood or are themselves myotoxic. Thus, the receipt of potentially interacting medications with statins is one of the factors that increase the risk of myopathy. The ACC/AHA/NHLBI clinical advisory on statins has listed the following medications as increasing the risk of statin-associated myopathy: fibrates, nicotinic acid, cyclosporine, azole antifungals, macrolide antibiotics, HIV protease inhibitors, nefazodone, calcium channel blockers, and amiodarone. This section gives a brief background on drug interactions followed by a description of prevalence and cost of co-prescription of statins with potentially interacting medications. Finally, the rationale, efficacy, and safety of concurrent use of statins with each class of potentially interacting medication will be described.

BACKGROUND ON DRUG INTERACTIONS

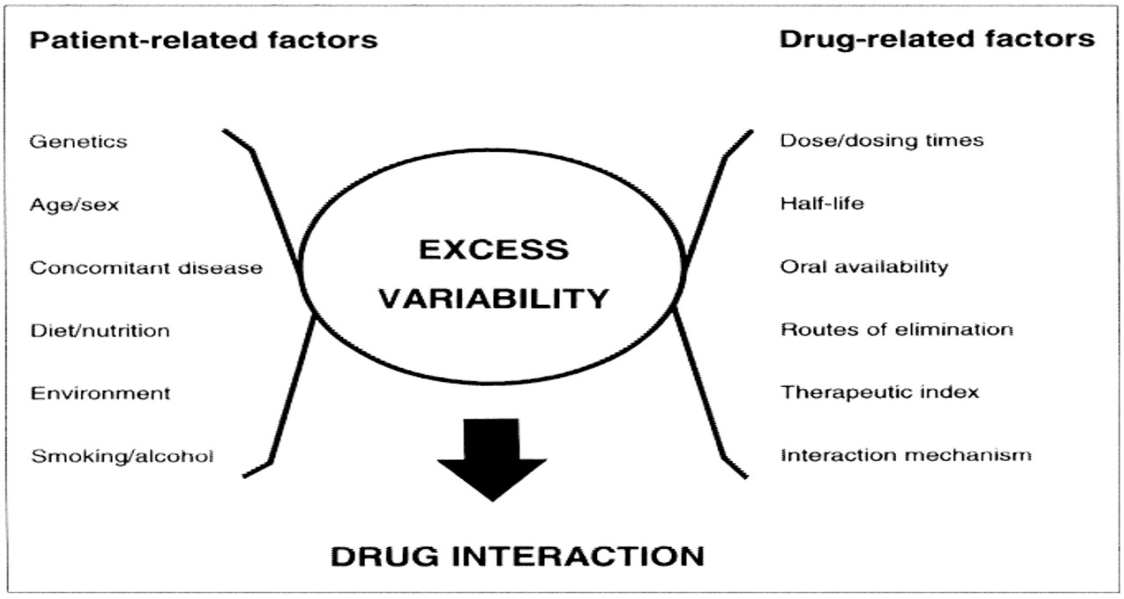
Drug-drug interactions are an important cause of adverse effects. Drug-drug interactions were responsible for approximately 5% of adverse effects in hospitalized patients.[206] Drug interactions can be either pharmacokinetic drug reactions or

[206] Ratz Bravo AE, Tchambaz L, Krahenbuhl-Melcher A, et al. Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. *Drug Saf* 2005;28:263-75.

pharmacodynamic drug reactions. Pharmacokinetic drug interactions occur when drugs cause an alteration in the concentration of unbound drug acting on the tissues. These interactions result in changes in drug absorption, metabolism or elimination. [207] Pharmacodynamic drug interactions are related to the pharmacologic activity of the interacting drug. These interactions are frequently associated with synergism, antagonism, or altered cellular transport. Pharmacodynamic interactions affect receptor sites and/or organ systems.[208]

The consequences of drug interactions depend upon patient-related as well as drug-related factors.[209] Figure 1.2 shows the factors that influence drug interactions.

Figure 1.2: Patient-related and drug-related factors influencing drug interactions



Source: Hansten PD. Understanding drug-drug interactions. *Science & Medicine* 1998;5:16-25.

[207] Herman RJ. Drug interactions and the statins. *CMAJ* 1999;161:1281-6.
[208] Brown CH. Overview of drug interactions. *US Pharmacist* 2000;25:25-35.
[209] Hansten PD. Understanding drug-drug interactions. *Science & Medicine* 1998;5:16-25.

As seen from Figure 1.2, the pharmacokinetic properties of a drug play a key role in occurrence of drug interactions. In addition, the dose/dosing times of the drug and the therapeutic index of the drug are also important considerations when a drug interaction occurs. Individual susceptibility to drug interactions (and thereby adverse reactions) because of age, genetics, or disease related factors (such as renal, hepatic) are also an important consideration. In summary, a variety of factors play a role in drug interactions.

STATINS AND DRUG INTERACTIONS

Drug interactions with statins can lead to serious adverse effects (rhabdomyolysis) which may result in death. The use of statins with potentially interacting medications has a higher risk of myopathy than statin monotherapy.[210] The mechanism of action of drug interaction involves CYP450 isoenzyme which is involved in metabolism of most statins as discussed earlier. CYP450 isoenzymes are also involved in the metabolism of many other drugs. Drug interactions occur when two or more drugs that are metabolized by the same CYP450 isoenzyme are given concurrently. Most statins are metabolized by CYP450 isoenzymes and bind weakly to these isoenzymes. As a result, drugs with stronger binding affinity for CYP450 isoenzymes will displace statins from these binding sites leading to increase in concentrations of statins in the blood.[211] This increases the risk of myopathy. In addition, pharmacodynamic interactions also can occur with statins leading to increase in the risk of myopathy.

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[210] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

[211] Bottorf M. Safety and statins: Pharmacologic and clinical perspective. *Am J Manag Care* 2004;4:S30-S37.

The possibility of drug interactions with statins is often unrecognized in clinical trials.[212] The probability of drug interactions is a particularly important consideration because of the high rates of polypharmacy among patients taking statins. Also, drug interactions with statins may have clinical and economic consequences. A few studies have been conducted that looked at the prevalence and cost of using statins with potentially interacting medications. The next section describes these studies.

PREVALENCE AND COST OF CO-PRESCRIPTION OF STATINS WITH POTENTIALLY INTERACTING MEDICATIONS

There have been very few studies that have described the prevalence and cost of use of statins with potentially interacting medications. One of the earliest studies investigating the co-prescribing of statins with potentially interacting drugs was conducted in Ireland. In this study, Heerey and colleagues used information from database from January to December 1998 to identify potentially interacting medications concurrently used with statins.[213] The results of this study showed that 34% of patients on simvastatin, 28% on atorvastatin and 16% on fluvastatin received medications with the potential for drug interactions. Recently, a Swiss study that assessed the prevalence of drug-statin interaction showed that about 6.9% of the population received potentially interacting medications that were harmful to the patients.[214]

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[212] Fine DM. Statin-related muscle toxicity. *Adv Stud Med.* 2003;3:554-560.
[213] Heerey A, Barry M, Ryan M, et al. The potential for drug interactions with statin therapy in Ireland. *Ir J Med Sci* 2000;169:176-9.
[214] Ratz Bravo AE, Tchambaz L, Krahenbuhl-Melcher A, et al. Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. *Drug Saf* 2005;28:263-75.

Petropoulos et al. looked at the frequency of simvastatin prescriptions with potentially interacting medications in Veterans Affairs health care system.[215] In this study, 10.5% of the patients were prescribed at least one potentially interacting medication. Approximately 57% of simvastatin doses were above the maximum recommended daily dose when prescribed with potentially interacting medications. A combination of high statin doses with potentially interacting medications increases the risk of myopathy. In another study conducted at a large U.S. managed care organization, approximately 32% of patients on simvastatin, 30% of patients on atorvastatin, and 3% of patients on pravastatin received a potentially interacting medication at some point.[216] The odds of receiving a potentially interacting medication were higher for both simvastatin and atorvastatin as compared to pravastatin. All of these studies reveal that statins are prescribed with potentially interacting medications quite often.

The economic consequences of concurrent use of statins and potentially interacting medications have also been studied. Einarson and colleagues[217] examined the effect of drug interactions with statins on Canadian health care costs. The results showed that the costs of hospital admissions, physician visits, and drugs were significantly higher for patients using statins and potentially interacting medications as compared to those using statins by themselves. In a U.S. study, patients' receiving potentially interacting

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[215] Petropoulos JB, Bello-Quintero CE. Frequency of simvastatin prescriptions with potentially interacting medications in a Veterans Affairs health care system. *J Manag Care Pharm* 2004;10:239-43.

[216] Etemad LR, Fairchild C, Waldeck R. *Prevalence and cost implications of potential interactions with statin medications in a managed care population.* ISPOR Ninth Annual International Meeting 2004. Washington, D.C.

[217] Einarson TR, Metge CJ, Iskedjian M, et al. An examination of the effect of cytochrome P450 drug interactions of hydroxymethylglutaryl-coenzyme A reductase inhibitors on health care utilization: a Canadian population-based study. *Clin Ther* 2002;24:2126-36.

medications had 32% greater medical costs and 50% greater pharmacy costs than those who did not receive any potentially interacting medications.[218]

In summary, all of the above-mentioned studies show that the prevalence and the costs of using statins with potentially interacting medications are high. With the potential for a substantial increase in the number of patients treated with statins over the next several years, the potential of drug interactions may further increase leading to a further increase in clinical and economic consequences. Therefore, it is important for health care professionals to be aware and prevent these interactions. The ACC/AHA/NHLBI clinical advisory on statins has listed the following medications as increasing the risk of statin-associated myopathy: fibrates, nicotinic acid, cyclosporine, azole antifungals, macrolide antibiotics, HIV protease inhibitors, nefazodone, calcium channel blockers, and amiodarone. The next part provides detailed information on interaction of each of the above-mentioned drugs with statins.

STATINS AND FIBRATES

Statins and fibrates have shown efficacy in clinical trials for reducing LDL and triglyceride levels, respectively (discussed earlier). Statins have also been shown to reduce the rate of cardiovascular events. In spite of this evidence, it has been shown in the clinical trials that the maximum reduction of cardiac events has been 40% comparing

[218] Etemad LR, Fairchild C, Waldeck R. *Prevalence and cost implications of potential interactions with statin medications in a managed care population.* ISPOR Ninth Annual International Meeting 2004. Washington, D.C.

statin with a placebo.[219] This means that there are a large number of people who in spite of being treated with statins experience a cardiac event. This is highlighted in the Scandinavian Simvastatin Survival Study where over a 5-year period 19% of drug treated patients experienced recurrent myocardial infarction or coronary death.[220] This may be due to increased triglycerides which also increase the risk of CHD.

Epidemiological studies suggest that hypertriglyceridemia, due to elevations of VLDL and IDL, is an independent risk factor for CHD.[221,222,223,224] The recent ATP III guidelines by NCEP recommend treatment beyond lowering LDL for patients with triglycerides of 200 mg/dl and above.[225] Therefore, if the triglycerides are above the recommended levels, the treatment plan for patients should include controlling high triglyceride concentrations. It is for this purpose that a combination therapy of statin with a fibrate is becoming a widely used treatment plan. However, statin and fibrate combinations are associated with increased risk of myopathy.[226,227,228] The following

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[219] Guyton JR. Combination drug therapy for combined hyperlipidemia. *Current Cardiology Reports* 1999;1:244-250.

[220] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.

[221] Austin M. Epidemiology of hypertriglyceridemia and cardiovascular disease. *Am J Cardiol* 1999;83:13F-6F.

[222] Jeppesen J, Hein HO, Suadicani P, et al. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. *Circulation* 1998;97:1029-36.

[223] Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation* 1992;85:37-45.

[224] Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* 1996;276:882-8.

[225] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.

[226] Shepherd J. Fibrates and statins in the treatment of hyperlipidaemia: an appraisal of their efficacy and safety. *Eur Heart J* 1995;16:5-13.

section will discuss studies that evaluated the efficacy and safety of statin-fibrate combination therapy.

Studies evaluating the efficacy and safety of statin and fibrate combination therapy

Many studies have assessed the efficacy and safety of combination therapy. The study designs of the published reports include randomized controlled trials, prospective open-label studies, and retrospective studies. Shek et al.[229] performed a thorough literature review of all studies evaluating combination therapy from 1988-2000. The authors reviewed 36 studies, of which 21 trials were open-label, six were retrospective, and 10 were prospective studies. A total of 1,674 patients were treated with combination therapy from two to 184 weeks. There were no cases of reported rhabdomyolysis; however, an incidence of 0.12% for myopathy (defined as CK levels greater than 10 times upper limit of normal (ULN)) was reported. A total of 1.9% of patients developed muscle weakness, musculoskeletal pain, or myositis. The authors pointed out that the true incidence might have been underestimated, because not all studies described the numbers or the reasons for discontinuation. One of the other reasons for low incidence rate may have been the controlled environment of some studies and extensive exclusion criteria which did not include a lot of high risk patients.

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[227] Shammas NW, Kapalis MJ, Deckert J, et al. Effectiveness of statin-gemfibrozil combination therapy in patients with mixed hyperlipidemia: experience of a community lipid clinic and safety review from the literature. *Prev Cardiol* 2003;6:189-94.

[228] Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA* 1990;264:71-5.

[229] Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001;35:908-17.

In a review of all randomized controlled trials, the author found an incidence rate of 1% of myopathy or rhabdomyolysis from such a combination.[230] Another study[231] pooled the data from prospective studies of statin-gemfibrozil combination therapy, and concluded that there was higher risk of myopathy in patients taking lovastatin-gemfibrozil combination (3.9%) compared to simvastatin-gemfibrozil (0.4%) combination therapy. Pierce et al.[232] reported similar high incidence rate (5%) with the use of lovastatin and gemfibrozil. Pravastatin-gemfibrozil combination seemed to be the safest among the three combinations with no reports of myopathy.[233]

A few studies that conducted head-to-head comparisons of different statin-fibrate combinations also have been published. Table 1.8 summarizes these studies that compared safety and efficacy of more than one statin-fibrate combination at the same time.

[230] Shepherd J. Fibrates and statins in the treatment of hyperlipidaemia: an appraisal of their efficacy and safety. *Eur Heart J* 1995;16:5-13.
[231] Shammas NW, Kapalis MJ, Deckert J, et al. Effectiveness of statin-gemfibrozil combination therapy in patients with mixed hyperlipidemia: experience of a community lipid clinic and safety review from the literature. *Prev Cardiol* 2003;6:189-94.
[232] Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA* 1990;264:71-5.
[233] Shammas NW, Kapalis MJ, Deckert J, et al. Effectiveness of statin-gemfibrozil combination therapy in patients with mixed hyperlipidemia: experience of a community lipid clinic and safety review from the literature. *Prev Cardiol* 2003;6:189-94.

Table 1.8: Study design, type and dose of statin and fibrate used, percent decrease in LDL and triglyceride levels, and number of patients with muscle symptoms and increase in CK levels in studies comparing different statin-fibrate combinations

Reference	Study Design	Patients (n)	Statin (mg)	Fibrate (mg)	% LDL Decrease	% Trig Decrease	Muscle Symptoms	Increase in CK (#)
Shammas et al (2003)[a]	Retro	46	Ator, sim, prav, cervi, flu	Gem 600	22	39	5	None
Athyros et al (2002)[b]	R	541	Prav 20, sim 20	Gem 1200, cipro 100	40	53	2	3
Taher et al (2002)[c]	Retro	106	Lov, prav, sim, flu, ator	Gem, Feno, Bez	35	44	7	3
Murdock et al (1999)[d]	Open label	252	Prav, sim, flu, lov, ator	Gem 1200	NA	41	7	1
Ellen et al (1998)[e]	Open label	80	Prav 20, Sim10	Fen 300	41	28	None	2

Table 1.8: Study design, type and dose of statin and fibrate used, percent decrease in LDL and triglyceride levels, and number of patients with muscle symptoms and increase in CK levels in studies comparing different statin-fibrate combinations (Continued)

Reference	Study Design	Patients (n)	Statin (mg)	Fibrate (mg)	% LDL Decrease	% Trig Decrease	Muscle Symptoms	Increase in CK (#)
Athyros et al (1997)[f]	R, DB	389	Prav 20, Sim 20	Gem 1200, cipro100	35-41	48-56	1	1

LDL-low density lipoprotein; CK-creatine kinase; Retro-retrospective; R-randomized; DB-double-blind; Ator-atorvastatin; Sim-simvastatin; Prav-pravastatin; Ceri-cerivastatin; Gem-gemfibrozil; Cipro-ciprofibrate; Feno-fenofibrate; Bez-bezafibrate; Trig-triglycerides; NA-not available.

[a.] Shammas NW, Kapalis MJ, Deckert J, et al. Effectiveness of statin-gemfibrozil combination therapy in patients with mixed hyperlipidemia: experience of a community lipid clinic and safety review from the literature. *Prev Cardiol* 2003;6:189-94.

[b.] Athyros VG, Papageorgiou AA, Athyrou VV, et al. Atorvastatin versus four statin-fibrate combinations in patients with familial combined hyperlipidaemia. *J Cardiovasc Risk* 2002;9:33-9.

[c.] Taher TH, Dzavik V, Reteff EM, et al. Tolerability of statin-fibrate and statin-niacin combination therapy in dyslipidemic patients at high risk for cardiovascular events. *Am J Cardiol* 2002;89:390-4.

[d.] Murdock DK, Murdock AK, Murdock RW, et al. Long-term safety and efficacy of combination gemfibrozil and HMG-CoA reductase inhibitors for the treatment of mixed lipid disorders. *Am Heart J* 1999;138:151-5

[e.] Ellen RL, McPherson R. Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. *Am J Cardiol* 1998;81:60B-65B.

[f.] Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, et al. Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial combined hyperlipidemia. *Am J Cardiol* 1997;80:608-13.

Although different statins were compared, none of the studies explicitly mentioned which statin-fibrate combination had more cases of myopathy. Only severe cases of myopathy were attributed to statin-fibrate combination therapy. A majority of the cases of rhabdomyolysis were associated with simvastatin and gemfibrozil. The dose of the drugs was not specified in some of the studies. But overall, these studies show that there are risks of muscle problems and an increase in CK levels.

In summary, statin-fibrate combination therapy seems to be therapeutically effective; however, there seems to be increased risk of myopathy when the two drugs are taken together. Due to different mechanisms of action, the interaction between statins and fibrates may appear to be pharmacodynamic but there is some evidence in the literature that the interaction may be due to pharmacokinetic interaction. The next section describes the pharmacokinetics of statin-fibrate combination therapy.

Effect of fibrates on pharmacokinetics of statins

As discussed previously (in Section I), both statins and fibrates monotherapy are independently associated with risk of myopathy. So a combination of two drugs together could explain the observed higher risk of muscle toxicity. Therefore, initial evidence pointed towards a pharmacodynamic reaction between the two drugs. In addition, fibrates are not known to inhibit CYP 450 mediated eliminations, and statins are not known to significantly inhibit any CYP pathways. This suggests lack of pharmacokinetic interaction between statin and fibrates. However, different pharmacokinetic studies evaluating the effect of fibrates on statins have had various conclusions. There have been

two studies conducted on simvastatin, pravastatin, and rosuvastatin, and one each on cerivastatin, atorvastatin, fluvastatin, and lovastatin evaluating the effects of fibrates on statin concentrations.

Bergman et al.[234] determined the effect of fenofibrate on simvastatin and simvastatin acid, which is the active form of simvastatin. Fenofibrate had no effect on pharmacokinetic parameters of simvastatin but the area under the curve (AUC) was decreased by 36% for simvastatin acid when the two were taken together. The mechanism of action by which the plasma concentrations was decreased was not known but the authors concluded that it would be safe to take the two drugs together. In contrast, the concurrent use of simvastatin with gemfibrozil increased the plasma concentrations of simvastatin. In particular, gemfibrozil increased the plasma AUC of simvastatin by 35% and that of simvastatin acid by 185%.[235]

Similar results have been observed with the administration of pravastatin with fenofibrate or gemfibrozil. Concomitant administration of fenofibrate and pravastatin did not affect the pharmacokinetics of pravastatin; however, the concentration of one of its metabolite 3α-iso-PV was increased by 26%.[236] The authors concluded that it was safe to take the two medications together even though there was a moderate increase in pravastatin metabolite. This increase should not raise clinical concerns as the metabolites have much lower pharmacological potency than pravastatin and lack of toxicity. On the

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[234] Bergman AJ, Murphy G, Burke J, et al. Simvastatin Does Not Have a Clinically Significant Pharmacokinetic Interaction With Fenofibrate in Humans. *J Clin Pharmacol* 2004;44:1054-1062.
[235] Backman JT, Kyrklund C, Kivisto KT, et al. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther* 2000;68:122-9.
[236] Pan WJ, Gustavson LE, Achari R, et al. Lack of a clinically significant pharmacokinetic interaction between fenofibrate and pravastatin in healthy volunteers. *J Clin Pharmacol* 2000;40:316-23.

other hand, concomitant administration of gemfibrozil and pravastatin increased AUC of pravastatin by 202%.[237] The authors attributed the increase, in part, to the decreased renal clearance of pravastatin in presence of gemfibrozil, and in part, to the increase of bioavailability of drug. The authors hypothesized that this increase in bioavailability may be due to the effect of gemfibrozil on transporting proteins, which are involved in absorption, tissue uptake and elimination of pravastatin.[238]

The concentration of rosuvastatin in presence of gemfibrozil increased 1.88-fold compared with placebo, and only minor increases in AUC of rosuvastatin were observed in presence of fenofibrate.[239,240] The authors concluded that the increase in rosuvastatin concentration in presence of gemfibrozil is due to inhibition of hepatic uptake of the statin by gemfibrozil.[241]

Most recently, Backman and colleagues[242] assessed the effect of gemfibrozil on atorvastatin. In a randomized crossover study, gemfibrozil increased the AUC of unchanged atorvastatin by 24%, and its active metabolites 2-hydroxyatorvastatin acid, and 4-hydroxyatorvastatin acid by 51% and by 82%, respectively. The authors concluded that only low doses of atorvastatin should be used with gemfibrozil, if necessary.

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[237] Kyrklund C, Backman JT, Neuvonen M, et al. Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther* 2003;73:538-44.
[238] Ibid.
[239] Schneck DW, Birmingham BK, Zalikowski JA, et al. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2004;75:455-63.
[240] Martin PD, Dane AL, Schneck DW, et al. An open-label, randomized, three-way crossover trial of the effects of coadministration of rosuvastatin and fenofibrate on the pharmacokinetic properties of rosuvastatin and fenofibric acid in healthy male volunteers. *Clin Ther* 2003;25:459-71.
[241] Schneck DW, Birmingham BK, Zalikowski JA, et al. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2004;75:455-63.
[242] Backman JT, Luurila H, Neuvonen M, et al. Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005;78:154-67.

Two studies evaluated the effect of gemfibrozil on earlier statins, fluvastatin and lovastatin. Contrary to most studies, gemfibrozil had no effect on plasma concentrations of fluvastatin,[243] and the combination therapy appeared to be safe. The plasma concentration of lovastatin acid, an active form of lovastatin, on the other hand, increased 280% compared to the placebo.[244] In the same study, bezafibrate had no effect on lovastatin concentrations, indicating it is safer to take lovastatin-bezafibrate combination than lovastatin-gemfibrozil combination.[245]

Lastly, the greatest effect of gemfibrozil is seen on the pharmacokinetics of cerivastatin as compared to any other statin. In a study conducted by Backman et al.,[246] gemfibrozil increased the plasma concentration of cerivastatin by 559%. In this study, the plasma concentrations of its metabolites also were increased vastly. The authors hypothesized that the increase in cerivastatin concentrations may be due to the effect on gemfibrozil on transporters that increase the absorption of cerivastatin,

In summary, statin-gemfibrozil combination increases the plasma concentration of statins, thus, increasing the risk of myopathy. In spite of this evidence, many clinicians continue to use this combination therapy together, and there have been many case reports of myopathy attributed to the use of statin and fibrates over the years. The next section discusses the FDA reports of myopathy due to statin-fibrate combination therapy.

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[243] Spence JD, Munoz CE, Hendricks L, et al. Pharmacokinetics of the combination of fluvastatin and gemfibrozil. *Am J Cardiol* 1995;76:80A-83A.
[244] Kyrklund C, Backman JT, Kivisto KT, et al. Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 2001;69:340-5.
[245] Ibid.
[246] Backman JT, Kyrklund C, Neuvonen M, et al. Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin Pharmacol Ther* 2002;72:685-91.

Myopathy/rhabdomyolysis reports in FDA database

FDA maintains a database of adverse events which is collected through voluntary reporting, as mentioned earlier (in Section III). Due to voluntary reporting by health care professionals, the quality of adverse event data may be inferior or incomplete as compared to clinical trials or well-controlled epidemiological studies; nevertheless, it may provide timely information about serious adverse events. This information can then be further used to scientifically design studies to monitor the safety of drugs.

Many researchers have analyzed FDA adverse event database to estimate reports on statin-fibrate associated rhabdomyolysis. Thompson et al.[247] did the most extensive study identifying all cases of rhabdomyolysis using FDA database between January 1, 1990 and March 31, 2002. A total of 3339 reports of rhabdomyolysis were related to statins of which 13% were due to statin-fibrate combination. This study did not break down the case reports by the type of statin-fibrate combination.

Chang et al.[248] reported the cases of rhabdomyolysis associated with the use of statins and gemfibrozil. The time period for this analysis was 1996 through July 31, 2001. Of a total of 866 cases of rhabdomyolysis, 482 cases (56%) were associated with statin monotherapy and 384 cases (44%) were associated with statin and gemfibrozil combination therapy. Approximately 92% of patients on statin-fibrate combination therapy were hospitalized and 6% of patients died. Little more than half the cases were

[247] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681-90.
[248] Chang JT, Staffa JA, Parks M, et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Saf* 2004;13:417-26.

female. Three-quarters of the rhabdomyolysis cases were associated with the use of cerivastatin and gemfibrozil.

Recently, Jones et al.[249] reviewed the database to determine the reporting rates of statins and fenofibrate versus statins and gemfibrozil. Fenofibrate resulted in fewer cases of rhabdomyolysis than gemfibrozil in combination with statins. This is not surprising as in-vitro studies have shown that gemfibrozil increases the plasma concentration of statins much more than fenofibrate.[250,251,252,253] Another similar study that assessed the risk of adverse events of all fibrates reported similar rates of rhabdomyolysis for both gemfibrozil and fenofibrate statin combination except for cerivastatin.[254]

These reporting rates using the FDA database may not reflect the true incidences of myopathy associated with statin-gemfibrozil therapy. The most important limitation of using the AERS database is the voluntary reporting. Therefore, it is important to conduct epidemiologic studies that can determine true incidence rates of myopathy due to statin-fibrate combination therapy. The next section describes these studies.

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[249] Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 2005;95:120-122.

[250] Bergman AJ, Murphy G, Burke J, et al. Simvastatin Does Not Have a Clinically Significant Pharmacokinetic Interaction With Fenofibrate in Humans. *J Clin Pharmacol* 2004;44:1054-1062.

[251] Backman JT, Kyrklund C, Kivisto KT, et al. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther* 2000;68:122-9.

[252] Kyrklund C, Backman JT, Neuvonen M, et al. Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther* 2003;73:538-44.

[253] Pan WJ, Gustavson LE, Achari R, et al. Lack of a clinically significant pharmacokinetic interaction between fenofibrate and pravastatin in healthy volunteers. *J Clin Pharmacol* 2000;40:316-23.

[254] Alsheikh-Ali AA, Kuvin JT, Karas RH. Risk of adverse events with fibrates. *Am J Cardiol* 2004;94:935-8.

Epidemiologic studies estimating the risk of myopathy due to statin fibrate combination therapy

The literature related to development of myopathy associated with the use statin and fibrates is sparse, with most attention on rhabdomyolysis. Only two known study has estimated the risk of myopathy in statin-fibrate combination therapy users.

Graham et al.[255] estimated the incidence of hospitalized rhabdomyolysis in users of statin-fibrate combination. The onset of symptoms occurred within 32 days of starting the combination therapy. According to the authors, the incidence rates of rhabdomyolysis for statin-fibrate combination therapy were much higher than statin monotherapy. The incidence rate for statin-fibrate combination therapy was 5.98 per 10,000 patient years except for cerivastatin-fibrate combination therapy. The risk of rhabdomyolysis with combined therapy was 12-fold higher than monotherapy. This risk was further increased in patients above 65 years old having diabetes. This study did not include lovastatin and fluvastatin users because there were very few users of these drugs.

In another study, the incidence of myopathy was 0.0 (95% CI: 0-19.5) per 10,000 person-years for statin-gemfibrozil combination and 5.19 (95% CI: 0.6-18.7) per 10,000 person-years for statin-fenofibrate combination therapy. Surprisingly, statin-fenofibrate combination had 4.32 times greater risk of myopathy than statin-only users. The risk was much lower for statin-gemfibrozil combination therapy.[256]

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[255] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.

[256] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.

In summary, there is evidence that the risk of myopathy increases with statin-fibrate combination use. Based on the literature review, there seems to be a difference in the risk of myopathy not only based on type of statin but also based on type of fibrate taken. There is a need to continuously monitor the outcomes when these two therapies are taken together.

STATINS AND NIACIN

Statins and niacin monotherapies are both effective in reducing cholesterol levels (discussed earlier). However, statins have only modest effects on increasing HDL levels (5%-10%).[257] This may be a problem in patients with high cholesterol and low HDL. Patients with combined hyperlipidemia have high LDL levels and/or high triglycerides and/or low HDL levels. As discussed earlier in the literature review, there is an inverse relationship between HDL levels and occurrence of CHD.[258,259] Therefore, it is important to raise HDL levels in patients with hyperlipidemia who have low HDL levels in addition to lowering LDL levels. Combination therapy with statin and niacin offers an attractive option to treat patients because the combination therapy offers the benefits of statins coupled with elevation of HDL levels and supplemental lowering of LDL and

[257] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-21.
[258] Castelli WP, Anderson K, Wilson PW, et al. Lipids and risk of coronary heart disease. The Framingham Study. *Ann Epidemiol* 1992;2:23-28.
[259] Boden WE. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data from Framingham to the Veterans Affairs High--Density Lipoprotein Intervention Trial. *Am J Cardiol* 2000;86:19L-22L.

triglycerides due to niacin. The next part describes the studies evaluating the efficacy and safety of combination therapy of statins and niacin.

Efficacy of statin-niacin combination therapy

The efficacy of statin-niacin combination therapy has been well established in various trials. In a multicenter randomized trial, combination therapy with simvastatin and niacin reduced LDL levels by 29% and triglycerides by 31%, and increased HDL levels by 31% after only 17 weeks of therapy.[260] In a review of clinical trials of combination therapy with statin (fluvastatin, lovastatin, or pravastatin) plus niacin, similar results were observed. The LDL levels were reduced by 25% to 57% and HDL levels were increased by 13% to 36%.[261] More recently, the HDL-Atherosclerosis Treatment Study[262] (HATS) showed a reduction in LDL levels by 42% and increase in HDL levels by 26% in patients with coronary disease, low HDL levels and normal LDL levels. All of the above evidence shows that treatment with combination therapy is effective.

Safety of statin-niacin combination therapy

The combination of statin and niacin is generally well-tolerated. Data from clinical trials in which patients received combination therapy do not report any cases of

[260] Miller M. Niacin as a component of combination therapy for dyslipidemia. *Mayo Clin Proc* 2003;78:735-42.
[261] Guyton JR, Capuzzi DM. Treatment of hyperlipidemia with combined niacin-statin regimens. *Am J Cardiol* 1998;82:82U-84U.
[262] Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583-92.

myopathy.[263,264] However, the number of patients in these trials was low. In another open-label study that evaluated the safety of the first combination drug containing extended-release niacin with lovastatin (Advicor®), there were no cases of myopathy; however, an increase in CK levels greater than five times upper limit of normal (ULN) occurred in 0.24% of patients.[265]

Nevertheless, case reports of myopathy have been reported in the literature though this relationship has not been well established. Niacin has been associated with rhabdomyolysis when administered with lovastatin, pravastatin or simvastatin but not with atorvastatin and fluvastatin.[266,267,268,269] In a recent study on statin-induced rhabdomyolysis using FDA adverse event database, only a few cases of rhabdomyolysis were associated with use of niacin and statins.[270] Despite the low rates of myopathy with concomitant use of niacin and fibrates, the ACC/AHA/NHBLI clinical advisory on use and safety of statins have recommended that health care professionals should use these two drugs together with caution until more evidence is available.[271]

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[263] Ibid.
[264] Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003;163:553-64.
[265] Rubenfire M. Safety and compliance with once-daily niacin extended-release/lovastatin as initial therapy in the Impact of Medical Subspecialty on Patient Compliance to Treatment (IMPACT) study. *Am J Cardiol* 2004;94:306-311.
[266] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288-95.
[267] Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. *Am J Cardiol* 1988;62:28J-34J.
[268] Garnett WR. Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am J Health Syst Pharm* 1995;52:1639-45.
[269] Reaven P, Witztum JL. Lovastatin, nicotinic acid, and rhabdomyolysis. *Ann Intern Med* 1988;109:597-8.
[270] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288-95.
[271] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

STATINS AND CALCIUM CHANNEL BLOCKERS

Many patients with hyperlipidemia may also have hypertension and may be receiving calcium channel blockers as antihypertensive drug therapy. Calcium channel blockers are weak inhibitors of CYP450 isoenzymes and may increase the plasma levels of statins, thereby increasing the risk of myopathy.[272] This was brought into focus when mibefradil, a strong inhibitor of CYP 3A4, was withdrawn from the market because of serious drug-drug interactions.[273] Several cases of statin-associated rhabdomyolysis were reported in patients receiving mibefradil.[274] Verapamil and diltiazem, which are weak inhibitors of CYP 3A4 isoenzymes, may pose a similar risk of statin-associated myopathy.

Pharmacokinetic effects of calcium channel blockers on statins

Drug interactions between statins and calcium channel blockers are pharmacokinetic drug interactions. This has been shown in various pharmacokinetic studies. In a randomized, double-blind, crossover study, the effects of verapamil, a calcium channel blocker, on the pharmacokinetics of simvastatin were studied in 12 healthy volunteers.[275] Verapamil increased the mean peak serum concentration of simvastatin 2.6-fold and the area under the plasma concentration-time curve (AUC) 4.6-

[272] Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004;94:1140-6.
[273] Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. *Circulation* 2004;109:50-57.
[274] Schmassmann-Suhijar D, Bullingham R, Gasser R, et al. Rhabdomyolysis due to interaction of simvastatin with mibefradil. *Lancet* 1998;351:1929-30.
[275] Kantola T, Kivisto KT, Neuvonen PJ. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998;64:177-82.

fold. The AUC of simvastatin increased in each subject. In addition, verapamil increased the peak concentrations of the active simvastatin acid metabolite 3.4-fold and the AUC 2.8-fold. In another open label study, similar results were obtained when verapamil was administered with pravastatin or simvastatin.[276]

The effects of diltiazem on the pharmacokinetics of lovastatin and pravastatin were studied in an open-label, 4-way crossover study in 10 subjects.[277] Each individual received a single dose of lovastatin or pravastatin with and without sustained-release diltiazem 120 mg twice daily during the 2 preceding weeks. Diltiazem did not affect the pharmacokinetics of pravastatin. In contrast, the AUC of lovastatin increased 257%, and the peak concentration increased 333%. In another study, diltiazem significantly increased the mean peak serum concentration of simvastatin by 3.6-fold ($p < 0.05$) and simvastatin acid by 3.7-fold ($p < 0.05$).[278] Diltiazem also significantly increased the area under the serum concentration-time curve of simvastatin 5-fold ($p < 0.05$) and the elimination half-life 2.3-fold ($p < 0.05$).

These studies show that there is a possibility of interaction between verapamil and diltiazem, and statins probably by inhibiting CYP 450 mediated metabolism, leading to increase in concentrations of statins in the blood which increases the risk of myopathy.

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[276] Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004;94:1140-6.
[277] Azie NE, Brater DC, Becker PA, et al. The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther* 1998;64:369-77.
[278] Mousa O, Brater DC, Sunblad KJ, et al. The interaction of diltiazem with simvastatin. *Clin Pharmacol Ther* 2000;67:267-74.

Evidence of statin and calcium channel blocker associated myopathy from clinical trials and practice settings

There have been two clinical trials, the 4S and HPS trials, in which some patients randomized to the statin group were also taking a calcium channel blocker. In the 4S trial, out of 668 patients in the simvastatin group who were taking a concomitant calcium channel blocker, only one patient developed myopathy after four years of therapy.[279] In the HPS trial, approximately 3000 patients randomized to the simvastatin group were taking calcium blocker. None of these patients developed myopathy.[280] The clinical trial evidence shows there is low risk of myopathy with use of statins and calcium channel blockers.

However, there have been case reports of myopathy in patients receiving calcium channel blockers and statins. At least six cases of rhabdomyolysis have been reported in patients receiving diltiazem and statins concurrently. Two of these cases were with atorvastatin[281,282] and four with simvastatin.[283,284,285] In some cases, preexisting renal dysfunction was present. Acute renal failure developed in five cases and required hemodialysis. Three patients died, and two patients recovered. Diltiazem was started one

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[279] Pedersen TR, Berg K, Cook TJ, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1996;156:2085-92.
[280] Gruer PJK, Vega JM, Mercuri MF, et al. Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. *Am J Cardiol* 1999;84:811-815.
[281] Lewin JJ, 3rd, Nappi JM, Taylor MH. Rhabdomyolysis with concurrent atorvastatin and diltiazem. *Ann Pharmacother* 2002;36:1546-9.
[282] Gladding P, Pilmore H, Edwards C. Potentially fatal interaction between diltiazem and statins. *Ann Intern Med* 2004;140:W31.
[283] Ibid.
[284] Peces R, Pobes A. Rhabdomyolysis associated with concurrent use of simvastatin and diltiazem. *Nephron* 2001;89:117-8.
[285] Mousa O, Brater DC, Sunblad KJ, et al. The interaction of diltiazem with simvastatin. *Clin Pharmacol Ther* 2000;67:267-74.

to three weeks prior to development of rhabdomyolysis in two patients. In other cases, there was a recent increase in the statin dose. In a review of the FDA database by Omar and Wilson,[286] case reports of rhabdomyolysis were observed with use of any statins and mibefradil. However, there were no reports from use of any other calcium channel blocker.

In summary, the evidence on the risk of myopathy associated with use of statins and calcium channel blockers is inconsistent and sparse. Health care professionals need to be aware and cautious when statins and calcium channel blockers are used together until more evidence is available to determine which patients are more susceptible to such interactions.

STATINS AND AMIODARONE

Amiodarone is an antiarrhythmic drug which is used to treat ventricular arrhythmias. Patients receiving amiodarone may also receive statins to control their cholesterol levels. Since amiodarone is mainly metabolized by CYP 450 isoenymes, it may decrease the metabolism of statins leading to an increase in concentration of statins in the blood, which may result in myopathy.[287] However, there are no known pharmacokinetic studies that have evaluated the effects of amiodarone on statin concentration in the blood. The ACC/AHA/NHBLI advisory on clinical use and safety of

[286] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288-95.
[287] Roten L, Schoenenberger RA, Krahenbuhl S, et al. Rhabdomyolysis in Association with Simvastatin and Amiodarone. *Ann Pharmacother* 2004;38:978-981.

statins listed amiodarone as one of the drugs that increases the risk of statin-associated myopathy.[288]

In an ongoing clinical trial, myopathy has been reported in 6% of patients receiving high dose simvastatin 80mg/day with amiodarone, according to the product information.[289] However, there was no increase in the frequency of myopathy in patients receiving simvastatin 20mg/day and amiodarone. Based on this information, the product labeling of simvastatin was changed, stating that dose of simvastatin should not exceed 20mg/day in patients concomitantly treated with amiodarone.[290] Similar drug interactions can be observed with other statins (as they are metabolized similarly) though there is no clear evidence of such interactions.

Recently, Alsheikh-Ali and colleagues[291] reviewed the adverse events reported to the FDA to determine the frequency of adverse events associated with concomitant use of statins (simvastatin, pravastatin, & atorvastatin) and amiodarone. The results showed that from 1990 through March 2002, there were 36 reports of adverse events related with simvastatin-amiodarone use, 29 reports of adverse events related to atorvastatin-amiodarone use, and only six reports related to pravastatin-amiodarone use. Most of these adverse events were muscle toxicity (76-77%), and occurred in older male patients who were on multiple other medications. The authors concluded that even though the frequency of muscle-related events was low, health care professionals have to be careful

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[288] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[289] Zocor. (simvastatin) [packcage insert]. Whitehouse Station, NJ: Merck & Co. Inc.; 2004.
[290] Ibid.
[291] Alsheikh-Ali AA, Karas RH. Adverse events with concomitant amiodarone and statin therapy. *Prev Cardiol* 2005;8:95-97.

when these two drugs are given together. Use of a statin not metabolized by CYP 450 isoenzyme (e.g. pravastatin) may be more appropriate in this scenario.[292]

As mentioned earlier, there are limitations to the AERS database and the results do not represent the true rates of myopathy. There have been no epidemiologic studies done evaluating the actual rates of myopathy associated with amiodarone-statin use. However, it is important to be cautious when using these drugs together until more evidence is available.

STATINS AND MACROLIDE ANTIBIOTICS

Macrolide antibiotics are used to treat a large number of bacterial infections. Patients receiving statins may obtain these antibiotics for short time period to treat infections. Macrolide antibiotics increase the levels of statins in blood by blocking statin metabolism.[293] This will increase blood levels of statin drugs and thus increase the risk of myopathy.

Pharmacokinetic studies assessing the effect of macrolide antibiotics on statins

There have been several pharmacokinetic studies conducted evaluating the effects of various macrolide antibiotics on statins. One of the earliest studies evaluated the effects of erythromycin on simvastatin in a randomized double-blind cross-over study.[294] The results of the study revealed that erythromycin increased the mean peak serum

[292] Ibid.
[293] Lee AJ, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. *Ann Pharmacother* 2001;35:26-31.
[294] Kantola T, Kivisto KT, Neuvonen PJ. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998;64:177-82.

concentration of simvastatin 3.4-fold and the AUC 6.2-fold. In another study, the effects of azithromycin and clarithromycin on atorvastatin were assessed in randomized open-label study.[295] The data demonstrated that azithromycin did not significantly alter peak serum concentrations of atorvastatin. Clarithromycin, on the other hand, increased the peak serum concentrations of atorvastatin by 56% and AUC by 88%. A comparative pharmacokinetic study which compared the effects of clarithromycin on pravastatin, simvastatin, and atorvastatin showed that there was a two-fold increase in concentration of pravastatin, five-fold increase in concentration of atorvastatin, and eight-fold increase in concentration of simvastatin when administered concomitantly with clarithromycin.[296] All these studies show that macrolide antibiotics, especially erythromycin and clarithromycin, interact considerably with statins. This is evident in case reports of myopathy due to concomitant use of statins and macrolide antibiotics.

Case reports of myopathy

There have been at least six published reports that provide evidence of interaction between various macrolide antibiotics and statins. Patients in three of the six case reports used clarithromycin,[297,298,299] two used erythromycin,[300,301] and one used azithromycin.[302]

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[295] Amsden GW, Kuye O, Wei GC. A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol* 2002;42:444-49.
[296] Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004;94:1140-6.
[297] Kahri AJ, Valkonen MM, Vuoristo MK, et al. Rhabdomyolysis associated with concomitant use of simvastatin and clarithromycin. *Ann Pharmacother* 2004;38:719.
[298] Lee AJ, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. *Ann Pharmacother* 2001;35:26-31.
[299] Grunden JW, Fisher KA. Lovastatin-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin. *Ann Pharmacother* 1997;31:859-63.

Prior to initiation of antibiotic therapy, patients did not report any signs or symptoms of myopathy. Following initiation of macrolide therapy, all patients had myopathy and elevated CK levels. Most of these patients were taking high doses of statins and some of them had renal impairment. These factors in addition to concomitant use of the two drugs together may have precipitated myopathy in these patients. In a review of the FDA database of adverse events over a 29-month time frame, 42 cases of rhabdomyolysis were associated with concomitant use of statins and macrolide antibiotics.[303] Based on this evidence, the ACC/AHA/NHLBI advisory on clinical use and safety of statins recommended avoiding the use of these two drugs together as it increases the risk of myopathy.[304]

STATINS AND AZOLE ANTIFUNGALS

Azole antifungals are used to treat fungal infections. Patients being treated with statins may simultaneously receive antifungals for treatment of such infections. The ACC/AHA/NHLBI advisory on clinical use and safety of statins states that use of statins with azole antifungals increases the risk of statin-associated myopathy.[305] Azole

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[300] Spach DH, Bauwens JE, Clark CD, et al. Rhabdomyolysis associated with lovastatin and erythromycin use. *West J Med* 1991;154:213-5.
[301] Ayanian JZ, Fuchs CS, Stone RM. Lovastatin and rhabdomyolysis. *Ann Intern Med* 1988;109:682-83.
[302] Grunden JW, Fisher KA. Lovastatin-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin. *Ann Pharmacother* 1997;31:859-63.
[303] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288-95.
[304] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[305] Ibid.

antifungals inhibit CYP 450 isoenzymes and thus decrease the metabolism of statins.[306] This can lead to increased concentrations of statins increasing the risk of myopathy.

Pharmacokinetic studies evaluating the effect of azole antifungals on statins

Pharmacokinetic studies have been conducted to assess the effects of azole antifungals on statins. In 12 healthy subjects, itraconazole increased the average serum concentrations of lovastatin acid (the active metabolite of lovastatin) 13-fold and the AUC 20-fold as compared to the placebo.[307] One subject experienced a 10-fold increase in plasma creatine kinase within 24 hours of lovastatin administration. Itraconazole increased the AUC of simvastatin 19-fold in 10 healthy subjects.[308] In contrast, the AUC of pravastatin increased less than 2-fold.[309] Itraconazole increased the AUC of atorvastatin and atorvastatin lactone between 2.5- and 4-fold.[310,311] Itraconazole had no effect on fluvastatin.[312] In 12 healthy volunteers, fluconazole increased the mean AUC of fluvastatin 81% and the mean C_{max} 44% but had no effect on pravastatin.[313] There have

[306] Shaukat A, Benekli M, Vladutiu GD, et al. Simvastatin-Fluconazole Causing Rhabdomyolysis. *Ann Pharmacother* 2003;37:1032-1035.
[307] Neuvonen PJ, Jalava KM. Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1996;60:54-61.
[308] Neuvonen PJ, Kantola T, Kivisto KT. Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clin Pharmacol Ther* 1998;63:332-41.
[309] Ibid.
[310] Kantola T, Kivisto KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther* 1998;64:58-65.
[311] Mazzu AL, Lasseter KC, Shamblen EC, et al. Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin. *Clin Pharmacol Ther* 2000;68:391-400.
[312] Kivisto KT, Kantola T, Neuvonen PJ. Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. *Br J Clin Pharmacol* 1998;46:49-53.
[313] Kantola T, Backman JT, Niemi M, et al. Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. *Eur J Clin Pharmacol* 2000;56:225-9.

been no known studies that have assessed the effect of ketoconazole on statins; however, case-reports of myopathy with all azole antifungals have been reported.

Case reports of myopathy

Rhabdomyolysis has been reported when statins have been taken with fluconazole,[314] itraconazole,[315,316] and ketoconazole.[317,318] Most of these patients were older patients with a history of multiple comorbidities and multiple medications. These factors may have further increased the risk of myopathy. Omar and Wilson reported 12 cases of statin-associated rhabdomyolysis in their review of FDA's adverse event database.[319] Thus, caution should be exercised when prescribing these two drugs together as it increases the risk of myopathy.

STATINS AND ANTIDEPRESSANT DRUGS

The antidepressant drugs such as fluxoetine, fluvoxamine, sertraline, and nefazodone inhibit CYP3A isoenzymes, and therefore should be cautiously used with

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[314] Shaukat A, Benekli M, Vladutiu GD, et al. Simvastatin-Fluconazole Causing Rhabdomyolysis. *Ann Pharmacother* 2003;37:1032-1035.
[315] Lees RS, Lees AM. Rhabdomyolysis from the coadministration of lovastatin and the antifungal agent itraconazole. *N Engl J Med* 1995;333:664-5.
[316] Horn M. Coadministration of itraconazole with hypolipidemic agents may induce rhabdomyolysis in healthy individuals. *Arch Dermatol* 1996;132:1254.
[317] Itakura H, Vaughn D, Haller DG, et al. Rhabdomyolysis from cytochrome p-450 interaction of ketoconazole and simvastatin in prostate cancer. *J Urol* 2003;169:613.
[318] Gilad R, Lampl Y. Rhabdomyolysis induced by simvastatin and ketoconazole treatment. *Clin Neuropharmacol* 1999;22:295-7.
[319] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288-95.

statins.[320] The clinical advisory on use and safety of statins listed only nefazodone as an antidepressant drug that may increase the risk of statin-associated myopathy.[321] This is because only case-reports of rhabdomyolysis associated with concurrent use of nefazodone and statins are known.

A pharmacokinetic study examined the potential for drug interaction when atorvastatin, simvastatin and pravastatin were each administered with nefazodone.[322] The results revealed a significant increase in the AUC of atorvastatin and simvastatin by 3.4-fold and 20-fold respectively. However, pravastatin concentrations were unaffected.

There have been some published case-reports of rhabdomyolysis associated with statin and nefazodone use.[323,324,325] All of these reports were due to concurrent use of simvastatin with nefazodone. However, in a study that reviewed the adverse events reported to FDA, a total four cases of rhabdomyolysis were reported, two of which were due to lovastatin.[326] Therefore, other statins metabolized the same way as simvastatin and lovastatin may also be susceptible to drug interaction with nefazodone. Therefore, health care professionals should be aware of this interaction until more evidence is available regarding patients at high risk.

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[320] Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 1996;153:311-20.
[321] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[322] Serzone (nefazodone). [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2004.
[323] Jacobson RH, Wang P, Glueck CJ. Myositis and rhabdomyolysis associated with concurrent use of simvastatin and nefazodone. *JAMA* 1997;277:296-7.
[324] Thompson M, Samuels S. Rhabdomyolysis with simvastatin and nefazodone. *Am J Psychiatry* 2002;159:1607.
[325] Skrabal MZ, Stading JA, Monaghan MS. Rhabdomyolysis associated with simvastatin-nefazodone therapy. *South Med J* 2003;96:1034-5.
[326] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288-95.

STATINS AND OTHER POTENTIALLY INTERACTING MEDICATIONS

Besides the interactions described above, there are published reports of interactions with thiazolidinediones,[327] phenytoin,[328] digoxin,[329] antithrombotic agents like warfarin,[330] and clopidogrel.[331] However, there is not enough evidence about the effects of co-administration of statins with these drugs to exclude their combination. Therefore, the ACC/AHA/NHBLI advisory on clinical use and safety of statins has not listed these medications as increasing the risk of myopathy when taken with statins.[332] However, patients should be started at low doses of statins and should be closely monitored until more evidence is available.

Cyclosporine and HIV protease inhibitors are other drugs that increase the risk of myopathy. A brief description of interactions of these potentially interacting medications with statins is outlined; however, these drugs will not be included in the study.

Statins and cyclosporine

Cyclosporine is used in patients with transplantation. In post-transplantation patients treating dyslipidemia is crucial because cardiovascular disease is a major cause

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[327] Alsheikh-Ali AA, Karas RH. Adverse events with concomitant use of simvastatin or atorvastatin and thiazolidinediones. *Am J Cardiol* 2004;93:1417-18.

[328] Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. *Circulation* 2004;109:50-57.

[329] Boyd RA, Stern RH, Stewart BH, et al. Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion. *J Clin Pharmacol* 2000;40:91-98.

[330] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288-95.

[331] Serebruany VL, Malinin AI, Callahan KP, et al. Statins do not affect platelet inhibition with clopidogrel during coronary stenting. *Atherosclerosis* 2001;159:239-41.

[332] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

of death in these patients.[333] Dyslipidemia often worsens during post-transplantation period, with increases in LDL levels and triglyceride levels. Because of the clinical benefit of statins, statin therapy is recommended with close follow-up. It is recommended low doses of statin therapy be used.[334]

The ACC/AHA/NHBLI advisory on clinical use and safety of statins lists cyclosporine as one of the medications that increases the risk of myopathy when taken with statins.[335] Cases of rhabdomyolysis have been reported in patients after transplantation taking cyclosporine with all statins except fluvastatin and pravastatin.[336,337,338,339] Texas Medicaid covers only very few transplantations that are deemed medically necessary. Therefore, there was very limited data on patients taking cyclosporine. Therefore, this drug was not included in the study.

Statins and HIV protease inhibitors

Dyslipidemia is a common problem in patients infected with HIV and receiving antiretroviral therapy. Abnormalities of lipid levels are associated with HIV infection

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[333] Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003;163:553-64.
[334] Ballantyne CM, Bourge RC, Domalik LJ, et al. Treatment of hyperlipidemia after heart transplantation and rationale for the Heart Transplant Lipid Registry. *Am J Cardiol* 1996;78:532-35.
[335] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[336] Corpier CL, Jones PH, Suki WN, et al. Rhabdomyolysis and renal injury with lovastatin use. Report of two cases in cardiac transplant recipients. *JAMA* 1988;260:239-41.
[337] Maltz HC, Balog DL, Cheigh JS. Rhabdomyolysis associated with concomitant use of atorvastatin and cyclosporine. *Ann Pharmacother* 1999;33:1176-9.
[338] Stirling CM, Isles CG. Rhabdomyolysis due to simvastatin in a transplant patient: Are some statins safer than others? *Nephrol Dial Transplant* 2001;16:873-4.
[339] Rodriguez JA, Crespo-Leiro MG, Paniagua MJ, et al. Rhabdomyolysis in heart transplant patients on HMG-CoA reductase inhibitors and cyclosporine. *Transplant Proc* 1999;31:2522-3.

itself as well as to antiretroviral therapy. The risk of coronary events appears to be increased in HIV-infected patients. Therefore, it is important to control dyslipidemia.[340]

Statins could be used effectively to control increased cholesterol levels. However, there is a potential for interaction between statins and protease inhibitors. Most protease inhibitors (indinavir, nelfinavir, ritonavir, and saquinavir) inhibit CYP3A metabolism.[341] This increases the risk of myopathy in patients receiving both drugs. Despite the increased risk, it is important to control the dyslipidemia to reduce the risk of coronary events. Therefore, statins and protease inhibitors are used together. To reduce the risk of myopathy the preferred statins are pravastatin or fluvastatin or change to non-CYP3A inhibitors antiretroviral therapy.[342] This study did not analyze the interaction between statins and protease inhibitors.

In summary, combination of statins with all the above-mentioned potentially interacting medications can increase the risk of myopathy. The concentration of statins in blood increases when potentially interacting medications are used together with statins. This increases the risk of myopathy. However, the magnitude of the risk varies depending on type of statin and potentially interacting medication used. Nevertheless,

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[340] Dube MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003;37:613-27.

[341] Davidson MH. Does differing metabolism by cytochrome p450 have clinical importance? *Curr Atheroscler Rep* 2000;2:14-9.

[342] Dube MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003;37:613-27.

caution should be exercised when using statins and potentially interacting medications together until more evidence is available.

SECTION V

RATIONALE FOR THE STUDY

Statins have become increasingly important in the management and prevention of coronary artery disease (CAD). Many clinical studies have shown the benefits of statin therapy for both primary and secondary prevention of CAD (as discussed in Section I). Statins are generally well-tolerated; however, the major side effect related to statin therapy is myopathy.

Myopathy is a general term referring to disorders of the muscles ranging from mild myalgia to severe rhabdomyolysis. The incidence of myopathy is between 0.1 percent and 5.0 percent depending on type and dose of statin, and severity of the condition.[343] However, this risk increases in presence of a number of factors.

The ACC/AHA/NHBLI advisory on the clinical use and safety of statins has identified a number of factors that increase the risk of statin-associated myopathy.[344] These include age, female gender, low body mass index, hypothyroidism, renal or hepatic dysfunction, diabetes mellitus, consumption of alcohol or grapefruit juice, and use of certain concomitant medications. Most of these risk factors were identified based on review of case reports. There have been very few studies, either clinical or epidemiological, that have confirmed these risk factors as being related to myopathy.

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[343] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[344] Ibid.

The recent guidelines recommend more aggressive treatment of elevated cholesterol levels.[345] This means that there will be a substantial increase in the number of people with the above-mentioned risk factors who will be treated with statin therapy over the next several years. Also, more people will receive higher statin doses and combination therapies to lower their cholesterol levels. In addition, many patients who are on statin therapy may also receive other medications to control their comorbidities. All of these factors increase the risk for statin-associated myopathy. However, the magnitude of the risk in the above-mentioned scenario is unknown. Therefore, it is important to conduct studies to identify the patients who are at higher risk of myopathy.

The general purpose of this study was to estimate the incidence and identify the risk factors for myopathy in patients receiving statins with and without potentially interacting medications using the Texas Medicaid database. The advantages and disadvantages of using databases for outcomes and pharmacoepidemiology studies are described in Appendix A. One study described the prevalence of myopathy in patients using statins with potentially interacting medications as 0.22%.[346] Cziarky and colleagues estimated the risk of myopathy to be six times higher in patients using statins and PIMs.[347] Another epidemiologic study estimated the risk of myopathy to be 12-fold

[345] Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.
[346] Shanahan RL, Kerzee JA, Sandhoff BG, et al. Low myopathy rates associated with statins as monotherapy or combination therapy with interacting drugs in a group model health maintenance organization. *Pharmacotherapy* 2005;25:345-51.
[347] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.

higher in patients using fibrates and statins than those who used only statins.[348] Most other studies have assessed only the relationship between myopathy and use of statins.

Given the sparse information in the literature about the risk and risk factors of myopathy, the current study aimed to fill this gap by identifying the risk factors for myopathy in the Texas Medicaid population. This information can be used by health care professionals to identify patients who are at higher risk of myopathy, and thus better manage their patients who are on multiple medications and have certain risk factors that predispose them to the risk of myopathy. By identifying patients early-on, health care professionals can improve clinical outcomes, and reduce the economic and humanistic burden associated with myopathy.

[348] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.

SECTION VI

GOALS, OBJECTIVES, AND HYPOTHESES OF THE STUDY

STUDY GOALS

The goals of this study were two-fold: 1) to evaluate trends in prescribing patterns of potentially interacting medications with statins and to identify factors that are associated with the receipt of potentially interacting medications; and 2) to evaluate the incidence and risk factors for myopathy in patients using statins and potentially interacting medications as compared to those using statins without potentially interacting medications. For the purpose of this study, patients who use statins and potentially interacting medications were called as **statin interacters** and patients who use statins without potentially interacting medications were called **statin users** (described in detail in the methodology chapter).

STUDY OBJECTIVES

The specific objectives for the above-mentioned goals were as follows:

<u>Evaluation of trends in prescribing patterns of potentially interacting medications with statins</u>

1) To provide descriptive statistics on type and dose of statins.
2) To provide descriptive statistics on the type and dose of potentially interacting medications.

3) To describe demographic characteristics of study population based on whether or not they receive potentially interacting medications.

4) To identify demographic, health-related, treatment, and physician-related factors that are associated with the receipt of potentially interacting medications with statins.

Evaluation of incidence and risk factors for myopathy in patients receiving statins with and without potentially interacting medications

5) To estimate the overall incidence of myopathy among study population.

6) To describe demographic characteristics of study population based on presence or absence of myopathy.

7) To describe the "time to occurrence of myopathy" in statin users and statin interacters.

8) To assess the relationship between the development of myopathy and use of potentially interacting medications with statins, while controlling for other risk factors for myopathy.

9) To determine the risk factors (demographic factors, health risk factors, and treatment factors) for myopathy.

STUDY HYPOTHESES

The specific study hypotheses for each of the goals were as follows:

Evaluation of trends in prescribing patterns of potentially interacting medications with statins

H_o1 There will be no difference in the odds of receipt of potentially interacting medication based on type of statin, while controlling for other factors.

H_o2 There will be no difference in the odds of receipt of potentially interacting medication based on dose of statin, while controlling for other factors.

H3 The odds of receipt of potentially interacting medication will increase with increasing age, while controlling for other factors.

H_o4 There will be no difference in the odds of receipt potentially interacting medication based on gender, while controlling for other factors.

H_o5 There will be no difference in the odds of receipt of potentially interacting medication based on ethnicity/race, while controlling for other factors.

H6 The odds of receipt of potentially interacting medication will increase with increasing number of comorbidities, while controlling for other factors.

H_o7 There will be no difference in the odds of receipt of potentially interacting medications based on physician specialty, while controlling for other factors.

Evaluation of incidence and risk factors for myopathy in patients receiving statins with and without potentially interacting medications

H8 The odds of developing myopathy will be higher for statin interacters as compared to statin users, while controlling for other factors.

H9 The odds of developing myopathy will increase with increasing age, while controlling for other factors.

H10 The odds of developing myopathy will be higher for females than males, while controlling for other factors.

H_o11 There will be no difference in the odds of developing myopathy based on ethnicity/race, while controlling for other factors.

H12 The odds of developing myopathy will be higher for patients with diabetes than those without diabetes, while controlling for other factors.

H 13 The odds of developing myopathy will increase with increasing number of comorbidities, while controlling for other factors.

H14 The odds of developing myopathy will be higher for patients using simvastatin as compared to pravastatin, while controlling for other factors.

H15 The odds of developing myopathy will be higher for patients using atorvastatin as compared to pravastatin, while controlling for other factors.

H16 The odds of developing myopathy will be higher for patients using fluvastatin/lovastatin as compared to pravastatin, while controlling for other factors.

H17 The odds of developing myopathy will be higher for patients on higher doses of statins than lower doses of statins, while controlling for other factors.

H18 The odds of developing myopathy will increase with increasing duration of use of statin, while controlling for other factors.

H19 The odds of developing myopathy will increase with increasing level of significance of drug interaction, while controlling for other factors.

H_o20 There will be no difference in the odds of developing myopathy based on whether the potentially interacting medication was given at the start of statin therapy or at a later date, while controlling for other factors.

H21 The odds of developing myopathy will increase with increased duration of potentially interacting medication use, while controlling for other factors.

H_o22 There will be no difference in the odds of developing myopathy based on physician specialty, while controlling for other factors.

CHAPTER 2

METHODOLOGY

There were two main goals of this study: 1) to evaluate trends in prescribing patterns of potentially interacting medications with statins and to identify factors that are associated with the receipt of potentially interacting medications; and 2) to evaluate the incidence and the risk of myopathy in patients using statins with and without potentially interacting medications. This chapter describes the methodology of the study. First, the study design is described followed by description of the patient population and patient selection criteria, study timeframe, study cohorts, and sample size calculations. Finally, the study variables and statistical analyses used for the study are outlined.

STUDY DESIGN

The current study utilized a retrospective cohort study design to address the goals. In a retrospective cohort study, cohorts of population are identified through a data source and followed over time looking for differences in the outcomes. A retrospective cohort study using an existing database is an efficient method for determining incidence rates.[349]

[349] Strom BL. *Study designs available for pharmacoepidemiology studies*. In: Strom BL, ed. Pharmacoepidemiology. London: John Wiley & Sons, Ltd., 2000:17-29.

PATIENT POPULATION AND PATIENT SELECTION CRITERIA

This study included patients enrolled in Texas Medicaid who received their prescription and medical benefits through this agency. The study cohort included patients between the ages of 21 years and 64 years. Patients 65 years and older were not included in this study since some patients may have dual eligibility (Medicaid and Medicare) resulting in incomplete medical information for these patients.

The patients selected were those who received their first statin prescription (new statin users) and were continuously enrolled for at least one year. Patients should not have used statin drug six months prior to their first pharmacy claim for a statin prescription. Patients using cerivastatin were excluded from the study due to market withdrawal of this drug. Patients who switched either a statin drug or dose or a potentially interacting medication during follow-up period were excluded from the study to obtain clean groups. Patients having renal insufficiency, hypothyroidism, and hepatic dysfunction were also excluded from the study because these patients have higher risk of myopathy associated with these conditions independent of statin use. Patients having HIV were excluded from the study. Also, patients having myopathy within six months prior to start of statin therapy or three months before index date (defined later) were excluded from the study in order to avoid attributing pre-existing myopathy to statin use.

The inclusion criteria for the study can be summarized as follows:

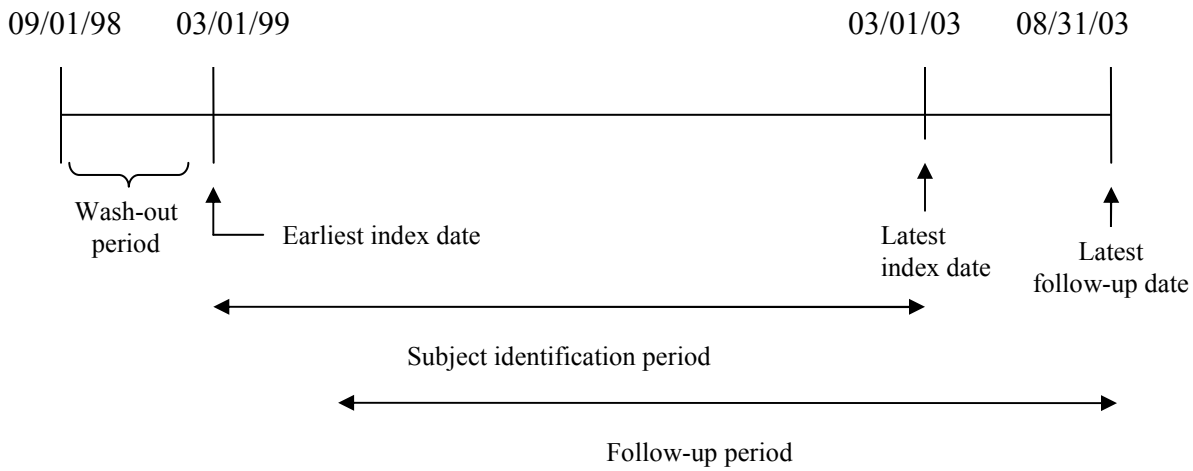
- Age group: 21-64 years;
- New statin users (no use of statin drug six months before the first statin prescription);

- At least one year continuous enrollment;
- No cross-over of statins or potentially interacting medication (i.e., no use of any other statin or PIM);
- No prescription for cerivastatin;
- No diagnosis of myopathy as identified by ICD-9-CM codes (Appendix B) within three months prior to index date ro six months before statin therapy;
- No diagnosis of renal insufficiency or hepatic dysfunction as identified by ICD-9-CM codes (Appendix B); and
- No diagnosis of hypothyroidism or HIV as identified by ICD-9-CM codes or use of hypothyroid or HIV drugs (Appendix B).

TIMEFRAME FOR THE STUDY

The overall timeframe of the study was from September 1, 1998 to August 31, 2003. A description of the study timeline is presented in Figure 2.1.

Figure 2.1: Timeline for the study



A wash-out period of six months was used to identify eligible patients based on the patient selection criteria mentioned above. Thus, the earliest observation date was March 1, 1999. The patients were followed six months from their index date. As discussed in literature review, most patients developed myopathy within two to four months of starting statin therapy with or without potentially interacting medications. Therefore, a time window of six months was chosen to capture the maximum number of cases of myopathy. The last follow-up date was August 31, 2003. The follow-up period will likely differ for each patient, as they enter or exit cohorts at different times.

Follow-up times were defined for each individual in person-months. The reporting of exposure time in aggregate person-months is considered meaningful as it takes into account the variable times of follow-up into estimating the incidence rate of myopathy. Patient follow-up ended when one the following occured: 1) diagnosis of

myopathy; 2) discontinued statin (a gap of 45 days or greater) therapy or PIM use; or 3) end of the six-month follow-up from the index date.

STUDY COHORTS

In the current study, two cohorts of patients were assembled. The first cohort consisted of patients who received statins without potentially interacting medications labeled as **statin users**. The second cohort consisted of patients who received statins with potentially interacting medications labeled as **statin interacters**. The list of potentially interacting medications is shown in Table 2.1.

Table 2.1: List of potentially interacting medications by therapeutic class contraindicated with statins used in the study

Therapeutic Class	Drugs
Fibrates	Gemfibrozil, Fenofibrate, Clofibrate
Nicotinic Acid	Niacin
Calcium Channel Blockers	Diltiazem, Verapamil
Antidepressant	Nefazodone
Antiarrthymic	Amiodarone
Azole Antifungals	Fluconazole, Ketoconazole, Itraconazole
Macrolide Antibiotics	Erythromycin, Clarithromycin, Azithromycin

Source: Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

As described in the literature review, the risk of myopathy increases when patients take the drugs listed in Table 2.1 along with statins. The reason is that the

interacting drug increases the concentration of statins in the blood, thereby increasing the risk of myopathy.

Cohort 1, the statin user

For the purpose of this study, a patient who received a statin drug without any potentially interacting medication was defined as a **statin user**. A statin user could receive any other medications besides the list of potentially interacting medications listed in Table 2.1.

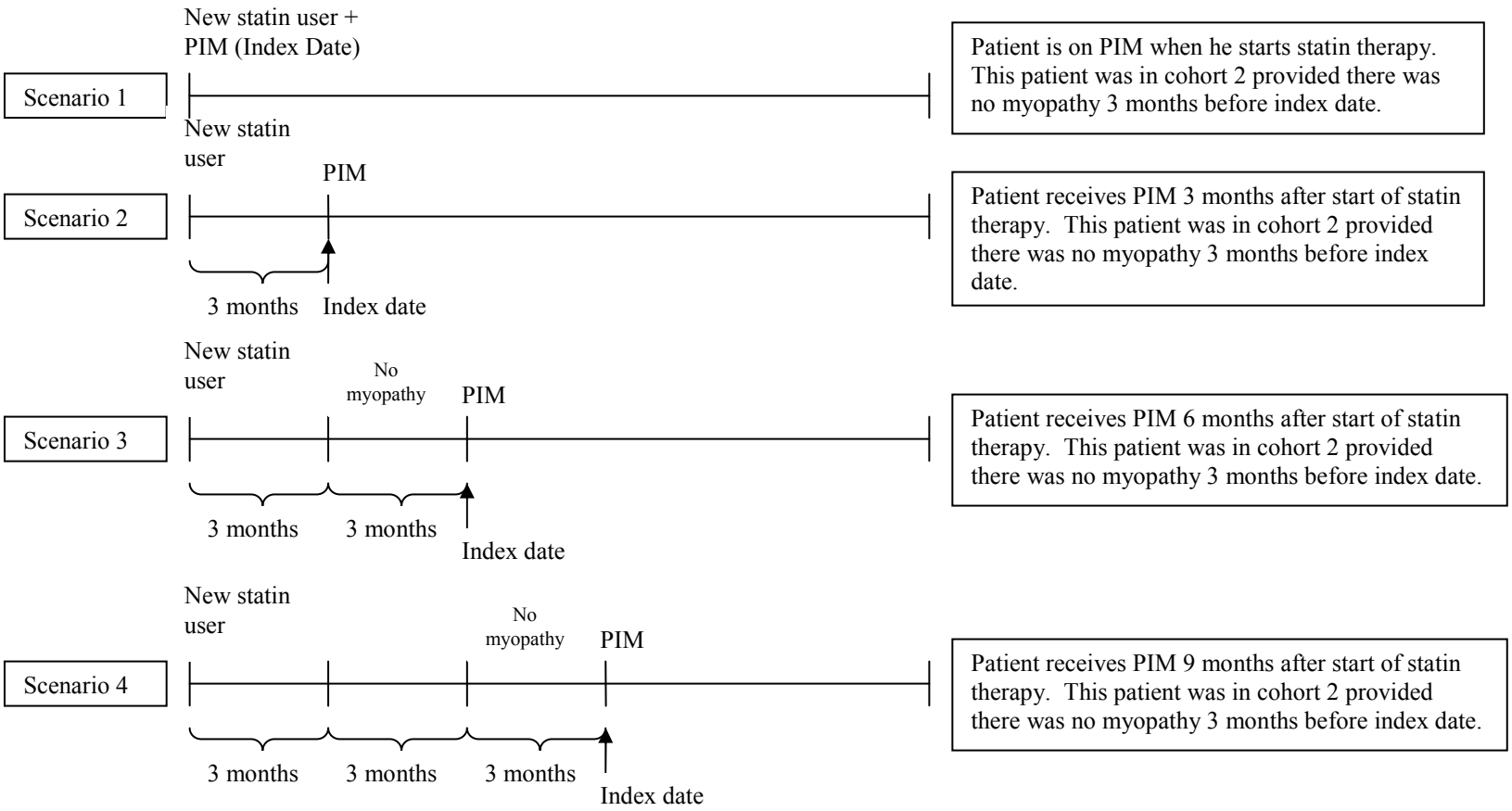
The index date for statin user was defined as the date of the first pharmacy claim for any statin starting from March 1, 1999. As mentioned before, only patients with no statin medication use six months prior to the first pharmacy claim for statin were included. The patients were followed until they experienced myopathy, discontinued statin therapy (a gap of 45 days or greater) or the follow-up period ended. A gap of 45 days was used to account for adherence and gaps between drug refills. Studies on compliance with statins have used similar gaps.[350,351,352] A sensitivity analysis was conducted using 60-day gap between drug refills.

[350] Andrade SE, Walker AM, Gottlieb LK, et al. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med* 1995;332:1125-31.
[351] Sung JC, Nichol MB, Venturini F, et al. Factors affecting patient compliance with antihyperlipidemic medications in an HMO population. *Am J Manag Care* 1998;4:1421-30.
[352] Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;288:455-61.

Cohort 2, the statin interacter

In this study, a patient who received a statin drug and potentially interacting medication (as listed in Table 2.1) simultaneously was defined as a **statin interacter**. The index date for a statin interacter was the date statin drug and potentially interacting medication were first received together. A PIM can be received at different time periods during the duration of statin use. Figure 2.2 demonstrates different scenarios when a potentially interacting medication can be received and a description of the different scenarios.

Figure 2.2: Description of scenarios based on the time a PIM was received



As seen from Figure 2.2, patients received PIMs at different times during the duration of statin use. As mentioned earlier, there should be no myopathy event three months before the index date, which for cohort two was the date the statin and potentially interacting medication were first received together. This is to be sure that the myopathy event was attributed to the concurrent use of statins and potentially interacting medications, and was not a carry-over effect from previous statin use. Statin interacters were followed from the index date until the patients experienced myopathy, or discontinued statin therapy (a gap of 45 days or more) or PIM use, or end of the follow-up period. A separate sub-group analysis was conducted on the statin interacter group to determine whether the risk of myopathy differed based on whether both statin and potentially interacting medication were received at the start of statin therapy or at a later date.

In summary, two multivariate analyses (discussed later) were conducted evaluating the risk factors of myopathy. In Model 1, statin users who never received any potentially interacting medications throughout the study period were compared with statin interacters. In Model 2, only the statin interacter group was included to evaluate the association of the level of significance of drug interaction and time/duration of potentially interacting medication and risk of myopathy.

In the original proposal, the method of assembling the two cohorts and the statistical analysis plan was different from what was conducted in the study. However this methodology was not followed. An explanation of this method and the reasons for not implementing the methodology has been described in Appendix C.

SAMPLE SIZE

To calculate sample size for a cohort study, information is required on the following five factors: 1) type I error rate (and whether it used for one-tailed or two-tailed statistical analysis); 2) power; 3) minimum relative risk; 4) incidence of outcome in the control group; and 5) ratio of cases to controls.[353]

Type I error rate (alpha level) was set at 0.05 level for all statistical analyses of the study. The power was set at 80% (a type II error rate of 20%). As discussed in the literature review, there has been only one known study directly comparing the risk of myopathy between statin users and statin interacters.[354] However, that study did not include all PIMs that were included in the current study. Therefore, on the basis of available epidemiological studies (as described earlier in literature review), and pharmacokinetic studies of statins with potentially interacting medications, a minimum relative risk of five was assumed when comparing the myopathy incidences between statin users and statin interacters.

The incidence of myopathy has been reported between <0.1-5.0 percent in clinical trials. For the purpose of this study, an incidence rate of 0.5% was assumed in the statin user group which is the comparator group for the statin interacter group and hence the control group in this study. The ratio of the control (statin user group) to the cases (statin interacter group) was set at 1:1.

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[353] Strom BL. *Sample size considerations for pharmacoepidemiological studies*. In: Strom BL, ed. Pharmacoepidemiology. London: John Wiley & Sons, Ltd., 2000:31-39.

[354] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.

Given the above information, the minimum required sample size can be calculated. The following formula was used to calculate sample size in cohort studies:[355]

$$N = \frac{1}{[p(1-R)]^2}\left[Z_{1-\alpha}\sqrt{\left(1+\frac{1}{K}\right)U(1-U)} + Z_{1-\beta}\sqrt{pR(1-Rp)+\frac{p(1-p)}{K}}\right]^2$$

Where p = the incidence of the disease in the unexposed (statin user group);

R = the minimum relative risk to be detected;

α = type I error rate;

β = type II error rate;

Z1- α and Z1- β = normal deviances from alpha and beta;

K = the ratio of controls to cases; and

U = $\frac{K\,p + p\,R}{K + 1}$ where K, p, and R are as defined before.

Based on the values of variables specified earlier and using the above equation, the number of subjects needed in the comparison groups was approximately 579 in a two-tailed analysis for the cohort study. Thus, a total minimum size of 1,158 was required for the study spilt equally between the two groups.

[355] Strom BL. *Sample size considerations for pharmacoepidemiological studies*. In: Strom BL, ed. Pharmacoepidemiology. London: John Wiley & Sons, Ltd., 2000:31-39.

INVESTIGATIONAL REVIEW BOARD APPROVAL

The investigational review board (IRB) of the University of Texas at Austin provided approval for the current study. The study did not involve direct contact with patients and the information was de-identified. However, since health information of patients enrolled in Texas Medicaid was used for the study, a petition was filed with the IRB to obtain a waiver of informed consent and was approved. As per the requirements of the waiver, the use of health information for this study involved minimal risk to the privacy of individuals as the study was a retrospective analysis of claims database and the researcher did not have access to personal names, social security numbers or addresses of the Medicaid patients.

DATA SOURCES

The data needed to conduct this study was collected from four data files. These files were obtained from the Texas Medicaid program and included the Texas Medicaid Eligibility File, the Texas Medicaid Medical Claims File, the Texas Medicaid Prescription Claims File, and the Texas State Board of Medical Examiners database. The databases were used to extract information on Medicaid eligibility of statin users, their demographic characteristics, statins and other potentially interacting medication use, diagnosis of myopathy as identified by ICD-9-CM codes and specialty of prescribing physician.

The Texas Medicaid Eligibility File

The Texas Medicaid Eligibility File contained information as presented in Table 2.2.

Table 2.2: Texas Medicaid eligibility file information

Data Fields
1. Unique client identification number
2. Date of birth
3. Gender of the patient
4. Ethnicity/race of the patient
5. Eligibility start date
6. Eligibility end date

The unique client identification number is a number that is assigned to each Medicaid patient and was used to link the eligibility file to the prescription and medical claims files. This number is unique for each patient and does not change from file to file.

The Texas Medicaid Prescription Claims File

The Texas Medicaid Vendor Drug program prescription claims file contained information about every prescription paid for by Texas Medicaid. Table 2.3 presents the data fields included in the prescription claims files.

Table 2.3: Texas Medicaid Prescription Claims File Information

Data Fields (Description)
1. Unique client identification number
2. Pharmacy provider number
3. Date prescription filled
4. Number of refills authorized
5. Prescribing physician number
6. Amount reimbursed by Medicaid
7. National Drug Code (NDC) (unique code for drugs that identifies the vendor, product, and package size)
8. Generic product sequence code (unique product code provided by First DataBank and assigned to all products having the same active ingredient and dosage form regardless of manufacturer)
9. Generic product identifier (classified drugs with respect to the compound indicator regardless of the strength)
10. Quantity dispensed
11. Days supply
12. Strength
13. Age of patient at prescription dispensing
14. Gender of patient

The prescribing physician number was used to link the prescription file with the Texas State Board of Medical Examiners database to identify the specialty of the physician.

The Texas Medicaid Medical Claims File

Medical resources used by Medicaid recipients who had medical claims from fee-for-service (FFS) and primary care case management (PCCM) are found in the Medicaid Medical Claims File. Data for only these FFS and PCCM patients were used in this study. Medicaid patients enrolled in plans that are paid on a capitation basis have

incomplete medical use data and thus were not employed in this study. Table 2.4 presents the information included in the medical claims file.

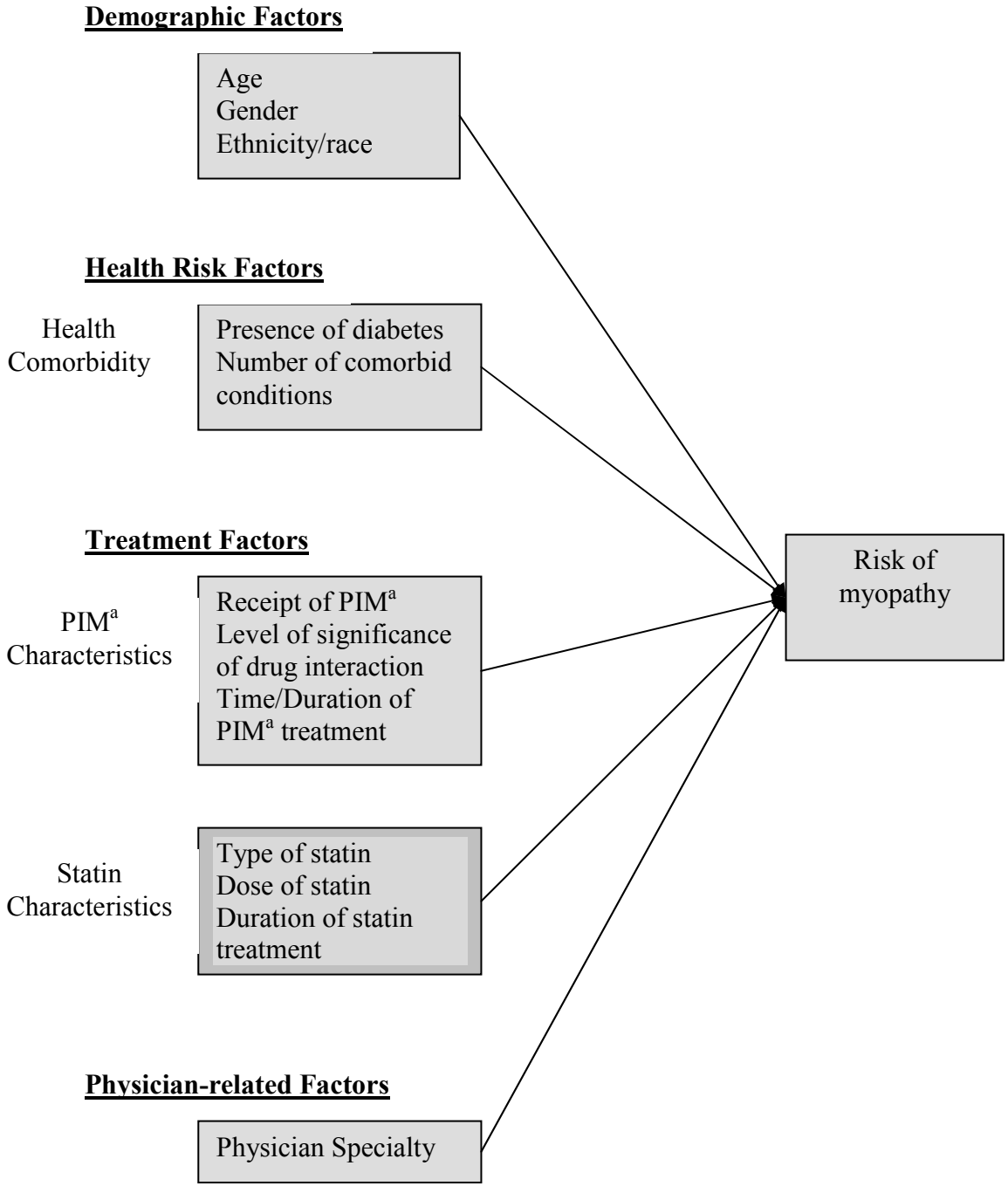
Table 2.4 Texas Medicaid Medical Claims File Information

Data Fields (Description/Definition)
1. Unique client identification number
2. Performing provider number
3. Diagnosis 1 (as identified by ICD-9-CM code)
4. Diagnosis 2 (as identified by ICD-9-CM code)
5. Diagnosis 3 (as identified by ICD-9-CM code)
6. Diagnosis 4 (as identified by ICD-9-CM code)
7. Diagnosis 5 (as identified by ICD-9-CM code)
8. Procedure code (as identified by CPT code)
9. Beginning date of service for the claim
10. Last date of service covered by the claim
11. Place of service (e.g., emergency room, inpatient hospital, physician's office, etc.)
12. Type of service (e.g., surgery, consultation, anesthesia, etc.)
13. Admit date
14. Admit diagnosis
15. Type of admission (e.g., emergency, newborn, etc.)
16. Days of service
17. Medicaid payment for the service
18. County code
19. DRG code of provider

STUDY VARIABLES

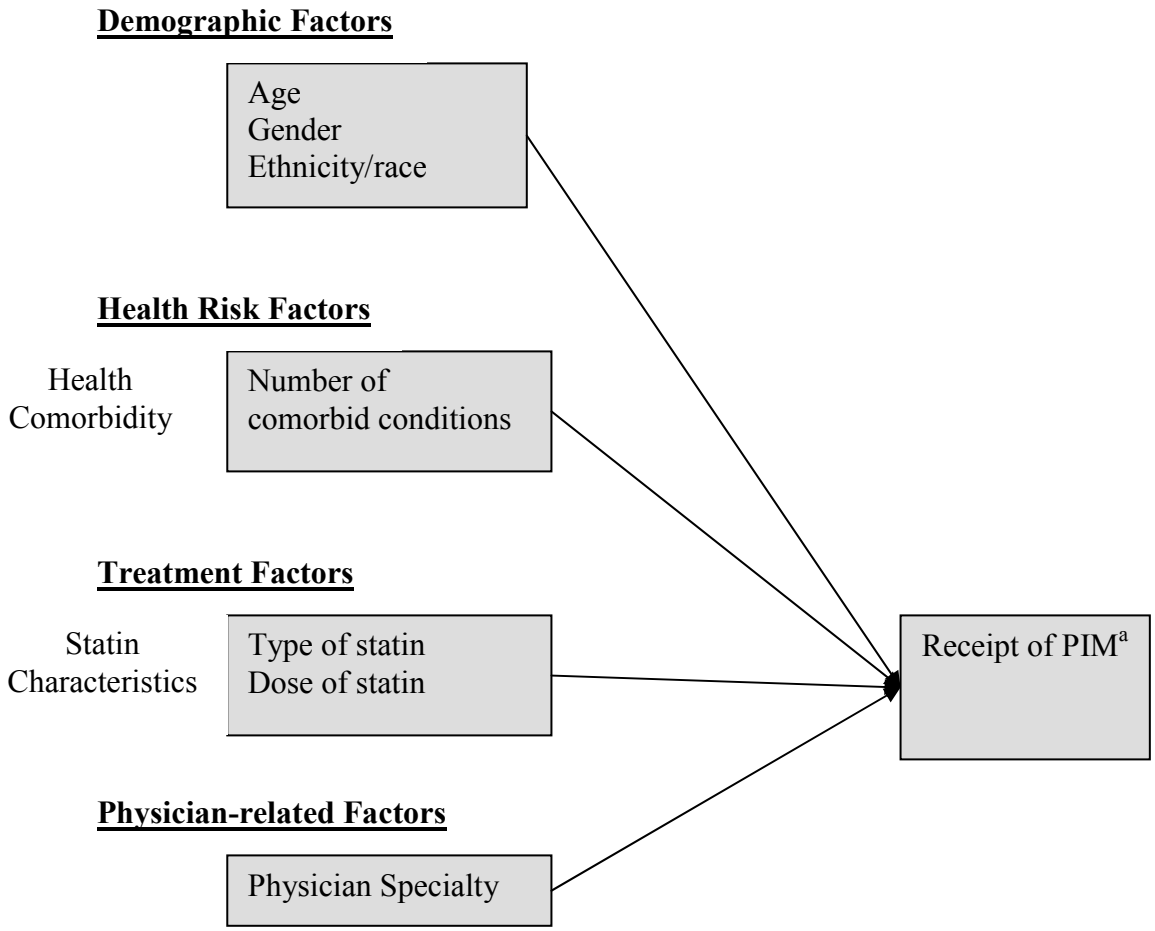
This section describes the study variables. First, the dependent variables are defined followed by the independent variables. Figure 2.3 and Figure 2.4 illustrate the conceptual models used in this study.

Figure 2.3: Study Model: Risk factors determining the risk of myopathy



[a.] PIM – Potentially interacting medication

Figure 2.4: Study model: Factors determining the odds of receiving a potentially interacting medication



a. PIM – Potentially interacting medication

Dependent variables / Study outcomes

The primary outcome of this study was the development of myopathy. The development of myopathy was a dichotomous variable (1 = presence of myopathy and 0 = absence of myopathy) and the log-likelihood of developing myopathy was the dependent variable. In addition, the duration of time to develop myopathy served as the study outcome in survival analysis.

Patients developing myopathy were identified using ICD-9-CM codes based on the following criteria:

- Primary or secondary diagnosis of myoglobinuria (ICD-9-CM code: 791.3);
- Primary diagnosis of myopathy (ICD-9-CM code: 359.4, 359.8, 359.9), myositis (ICD-9-CM code: 729.1), polymyositis (ICD-9-CM code: 710.4), muscle weakness (ICD-9-CM code: 728.9), other disorders of muscle, ligament, and fascia (ICD-9-CM code: 728.89), musculoskeletal symptoms of the limbs (ICD-9-CM code:729.81, 729.82, 729.89) or adverse effect from antihyperlipidemic agents (ICD-9-CM code:E942.2);
- A secondary diagnosis of muscle-related disorder (as mentioned above) plus a laboratory claim for serum creatine kinase measurement within seven days of the diagnosis; and
- A primary diagnosis of acute renal failure (ICD-9-CM code: 584.0) plus a secondary diagnosis of muscle-related disorder or a laboratory claim of serum creatine kinase measurement within seven days of the diagnosis.

The identification of cases of myopathy based on the above criteria has been validated before. Andrade et al.[356] conducted a retrospective study and evaluated positive predictive values (PPVs) for identification of cases of myopathy and rhabdomyolysis based on ICD-9-CM codes. The criteria used to identify cases of myopathy were the same as used in this study. PPV was calculated as percentage of confirmed cases identified using administrative databases. A composite PPV of 74% was estimated using the first three criteria. The authors concluded that the ICD-9-CM codes and laboratory claims data can facilitate identification of myopathy cases.

The other study outcome was whether or not a patient received potentially interacting medications (receipt of potentially interacting medication). The receipt of potentially interacting medication was a dichotomous variable (1 = receipt of PIM and 0 = no receipt of PIM) and the log-likelihood of receiving a potentially interacting medication served as a dependent variable.

Independent variables

Risk factors for developing myopathy and receipt of potentially interacting medication were included in the analysis as covariates. These risk factors have been discussed in detail in the literature review. The risk factors were classified into four main categories: demographic factors, health risk factors, treatment factors, and physician-related factors. Each of these risk factors are operationally defined in the next section.

[356] Andrade SE, Graham DJ, Staffa JA, et al. Health plan administrative databases can efficiently identify serious myopathy and rhabdomyolysis. *J Clin Epidemiol* 2005;58:171-4.

Demographic factors:

Three demographic factors that were included in the study were age, gender, and ethnicity/race. The demographic factors are explained in Table 2.5.

Table 2.5: Explanation of demographic factors used in the study

Variable	Explanation/Definition
Age	Age was defined as the age of person in years at the index date. Age was analyzed as a continuous variable.
Gender	Gender was a dichotomous variable and was indicated as male or female. Male was used as the reference category.
Ethnicity/race	Ethnicity/race was coded as Whites, Blacks, Hispanics, Asians, and others. Whites was used as the reference category.

Health risk factors

There are two main health risk factors that may increase risk of myopathy: lifestyle factors and comorbidity factors. For the purpose of this study, information on lifestyle factors such as physical activity, body size, and consumption of grape-fruit juice and alcohol were not available for the study, which was a limitation of the study. In this study, two factors related to comorbidities of patients were included in the analysis.

Health comorbidity factors

The presence of renal insufficiency, hypothyroidism, and hepatic dysfunction poses a risk of myopathy independent of statin use. Therefore, patients with these

conditions were excluded from the study. The two health comorbidity variables included in the study were presence of diabetes and number of comorbid conditions.

Diabetes

Diabetes is considered to be a risk factor for myopathy. As mentioned in the literature review, diabetes patients have reduced drug metabolism thereby increasing the concentration of statin drug in the blood. This increases the risk of myopathy.

Presence or absence of diabetes was coded as a dichotomous variable where 1=diabetes and 0= no diabetes. ICD-9-CM codes (ICD-9-CM codes: 250.xx) and use of anti-diabetic drugs were used to identify patients having diabetes.

Number of comorbidities

Presence of comorbid conditions may increase the likelihood of receiving potentially interacting medications, which in turn, can increase the risk of myopathy. Therefore, it is important to include a covariate that controls for the number of comorbid conditions in patients.

The total number of comorbidities present at or prior to start of statin use was calculated. The list of clinical conditions and the ICD-9-CM codes are shown in Table 2.6. The list of clinical conditions and the ICD-9-CM codes were adapted from the Deyo et al. version of Charlson comorbidity index using ICD-9-CM codes.[357,358] Patients with renal disease, liver disease and HIV infection were excluded from the current study. Therefore, these clinical conditions were not included in the calculation of the number of

[357] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
[358] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613-9.

comorbidities. Also, diabetes was controlled for separately as a covariate and was not included in the list of comorbid conditions.

Table 2.6: Major clinical conditions and ICD-9-CM codes used to define comorbidities based on the Charlson comorbidity index

Clinical Conditions	ICD-9-CM codes
Myocardial infarction	410.xx, 412
Congestive heart failure	428.xx, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93
Peripheral vascular disease	441.x, 443.9, 785.4, V43.4, 38.48
Cerebrovascular disease	430-437.x, 438
Dementia	290.x
Chronic pulmonary disease	490-496, 500-505, 506.4
Connective tissue disease	710.0-710.1, 710.4, 714.0-714.2, 714.81, 725
Ulcer disease	531.0x-531.7x, 532.0x-532.7x, 533.0x-533.7x, 534.0x- 534.7x, 531.9, 532.9, 533.9, 534.9
Hemiplegia	342.x, 344.1
Any tumor, including lymphoma, leukemia	140.x-172.x, 174.x-195.x, 200.xx-208.xx
Metastatic solid tumor	196.x-199.x

Sources: 1) Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chron Dis* 1987;40:373-383.
2) Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613-619.

Treatment factors

Treatment factors are important factors in evaluating the risk of myopathy. Both characteristics of statins as well as PIMs were included in the study models; however, only statin characteristics (type of statin therapy and dose of statin therapy) were included in determining the odds of receiving a potentially interacting medication. Operational definitions and explanation of these variables are described below.

Receipt of potentially interacting medication

As discussed in section four of the literature review, the risk of myopathy greatly increases with concurrent administration of statin and potentially interacting medications. The list of potentially interacting medications is shown in Table 2.1. This is an important variable among treatment factors that influences the risk of myopathy. As described before, there were two study cohorts: **statin users** (defined as patients who received statins without potentially interacting medication), and **statin interacters** (defined as patients who received statins with potentially interacting medication). This variable was a dichotomous variable where 1 = someone who received potentially interacting medication (statin interacter) and 0 = someone who did not receive a potentially interacting medication (statin user). The statin user cohort was the reference category.

Level of significance of drug interaction

The risk of myopathy may vary based on the type of potentially interacting medication received. Interactions of some potentially interacting medications with statins may be more severe than the others. The reference, Drug Interaction Facts, was used to assign a level of significance to drug interactions.[359] The following scale was used:

- Level 1 was defined as a potentially severe or life-threatening interaction, and was coded as 0 and was the reference category.
- Level 2 was defined as an interaction that may cause detoriation in patients' clinical status, and was coded as 1.

[359] Drug Interaction Facts. Wolters Kluwer Health, Inc, 2003-2005. Available at: http://www.efactsonline.com/Fac/servlet/MainPage. Accessed on: January 2005

- Level 3 was defined as an interaction that may cause moderate to minor side effects, and was coded as 2.

Table 2.7 provides the list of PIMs based on level of drug interaction significance.

Table 2.7: List of PIMs[a] by level of drug interaction significance

Level of Significance of Drug Interaction	Type of PIM[a]
Level 1[b]	Fibrates, Antidepressants, Antibiotics
Level 2[c]	Calcium Channel Blockers, Antifungals
Level 3[d]	Nicotinic acid, Amiodarone

a. PIM – Potentially Interacting Medication
b. Level 1 is defined as potentially severe or life threatening interaction.
c. Level 2 is defined as interaction that causes detoriation in patients' clinical status.
d. Level 3 is defined as moderate to minor side effects.

Type and dose of statin

As discussed in the literature review, the pharmacokinetic properties and doses differ across statins and this affects the risk of myopathy. Therefore, it is vital to include these variables in the analysis. The type of statin was coded into five categories where 0 = pravastatin, 1 = atorvastatin, 2 = simvastatin, 3 = lovastatin and 4 = fluvastatin. Pravastatin was the reference category as it is the only statin which is not metabolized by the cytochrome P450 system.

The doses of statins were categorized into two groups. Table 2.8 shows the two groups which are formed based on the comparative efficacy of the statins on lipid levels.

All the doses in group I were lower (coded as 0) and have lower reduction in lipid levels as compared to doses of statins in group II (coded as 1).

Table 2.8: Grouping of statin doses based on statin efficacy

Group	Statin Drug and Dose (mg)[a, b]				
	Atorvastatin	Simvastatin	Pravastatin	Lovastatin	Fluvastatin
I	- 10 mg	10 mg 20 mg	20 mg 40 mg	20 mg 40 mg	40 mg 80 mg
II	20 mg 40 mg 80 mg	40 mg 80 mg -	- - -	80 mg - -	- - -

Source: Maron DJ, Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000;101:207-13.
[a] Rosuvastatin was not included because the drug was not approved for the time period of this study.
[b] Cerivastatin was not included, because the drug was withdrawn and these patients are excluded in this study.

Duration of statin treatment

Duration of statin use may affect the risk of myopathy. This variable captured the time period a patient was exposed to statin treatment before experiencing an event. Duration of statin treatment was defined as the number of days of statin treatment in the observation period. The formula to calculate duration of statin use was as follows:

Duration of statin treatment = Σ Days supply (as listed on Rx claim)

The date for the first statin prescription was the date to start calculating days supply. The last date of statin prescription was defined as: 1) discontinuation of statin therapy (a gap of 45 days or greater); or 2) patient experiences myopathy; or 3) end of study's follow-up period. Duration of statin use was the sum of days' supply between the

first and last date of statin prescription. A sensitivity analysis was conducted using a 60-day gap between refills.

Time/Duration of PIM use

Time/Duration of PIM use may also affect the risk of myopathy. These variables were included in a separate analysis which included only statin interacters to determine if these variables affect myopathy. Time of PIM use was a dichotomous variable where 1 = PIM use at start of statin therapy and 0 = PIM use at a date later than the date of start of statin therapy. Duration of PIM use was defined as the number of days of PIM use in the observation period before a patient experiences an event or end of PIM use.

Physician-related factors

There was only one variable included in this factor, namely physician specialty.

Physician specialty

Physician specialty is an important factor to be included in the models. Some physicians may be more aware of drug interactions than others. It may also happen that patients of certain physician specialties may experience fewer myopathy events than others due to greater awareness of risk factors. Therefore, this variable was included in the second model too. Physician specialty was defined as the prescribing physician at index date. The specialty was coded into three groups: 0 = general practice/family practice and internal medicine, 1 = cardiologists and 2 = others.

In summary, a number of independent variables were included in the two models. Some of the variables were continuous whereas others were categorical variables. Table 2.9 illustrates the coding scheme and definition of all the dependent and independent variables.

Table 2.9: Coding scheme and definition of dependent and independent variables

Variable Type	Variables	Coding scheme[a]	Definition
Dependent variable	Receipt of PIM	0 1	No Yes
	Occurrence of Myopathy	0 1	No Yes
	Time to Myopathy event	Continuous (Days)	Time lapse between index date and event date or censor date
Independent Variables – Demographic factors	Age	Continuous (Years)	Age at the index date
	Gender	0 1	Male Female
	Ethnicity/race	0 1 2 3 4	Whites Blacks Hispanics Asians Others
Independent variables – Health Comorbidity factor	Presence of diabetes	0 1	No Yes
	Number of comorbidities	Count (e.g. 0, 1, etc.)	Total number of comorbidities at or prior index date.

Table 2.9: Coding scheme and definition of dependent and independent variables (Continued)

Variable Type	Variables	Coding scheme[a]	Definition
Independent Variables – Treatment Factors	Receipt of PIM	0 1	Statin User only Statin Interacter
	Significance of drug interaction	0 1 2	Level 1 Level 2 Level 3
	Duration of statin treatment	Continuous (days)	Sum of days supply between first and last date of statin Rx.[b]
	Duration of PIM use	Continuous (days)	Days of PIM use concurrent with statins
	Time of PIM use	1 0	PIM use at index date PIM use post-index date
Independent variables – Physician-related factors	Physician Specialty	0 1 2	General practice/family practice/ internal medicine Cardiologists Others[c]

[a.] 0 is the code for the reference category
[b.] Formula to calculate duration discussed in study variables section
[c.] All other specialty except those mentioned above.

STATISTICAL ANALYSES

Based on whether a patient receives a potentially interacting medication with a statin, patients were categorized into two groups, statin users and statin interacters, as described previously in the study cohort section. These two groups were compared to determine the factors that influence the odds of receiving a potentially interacting medication, and the incidence and risk factors for development of myopathy.

Data manipulation and statistical analyses were conducted using SAS version 9.1 and Statistical Packages for the Social Sciences (SPSS) v. 12.0. The *a priori* level of significance was 0.05 for all statistical tests. All tests were two-tailed unless otherwise specified.

Descriptive analyses (frequencies, means, and standard deviations) were used to examine the demographics (age, gender, and ethnicity/race) of the subjects. Similarly, frequency distributions of the type and dose of statins and potentially interacting medications used were conducted. Descriptive analyses were used to evaluate the overall incidence (incidence density) of myopathy among Medicaid patients. Time to development of myopathy was estimated using the Kaplan-Meier procedure.

Logistic regression was used to assess the factors that influence the receipt of potentially interacting medications. In order to evaluate the risk factors of myopathy, two separate multivariate models were tested as mentioned earlier in study cohort section. In Model 1, statin users who never received any potentially interacting medications throughout the observation period were compared with statin interacters. In Model 2, only the statin interacter group was included to evaluate the effect of time/duration of potentially interacting medication on the risk of myopathy. For both of these models, logistic regression was used.

Analyses for the study objectives

There were two main goals of the study: 1) to evaluate trends in prescribing patterns of potentially interacting medications with statins and to identify factors that are

associated with the receipt of potentially interacting medications; and 2) to evaluate the incidence and the risk of myopathy in patients using statins with and without potentially interacting medications. The statistical analyses used for the objectives of each of the goals are described below.

Evaluation of trends in prescribing patterns of potentially interacting medications with statins

Objective 1: To provide descriptive statistics on the type and dose of statins.

Frequencies and percentages were used to describe the type and dose of statin used.

Objective 2: To provide descriptive statistics on the type of potentially interacting medications

Frequencies were calculated to address Objective 2. In addition, the potentially interacting medications were classified based on level of significance of drug interaction with statins, as described previously. Frequencies were used to classify the drug interactions into three levels of significance.

Objective 3: To describe demographic characteristics of the study population based on whether or not they receive potentially interacting medications.

Descriptive statistics (frequencies, mean, variance) were calculated for the analysis of Objective 3. Demographic characteristics such as age, gender, and

ethnicity/race were described using means, frequencies and standard deviations. Patients were classified separately based on whether or not they receive potentially interacting medications and descriptive statistics for each group were presented separately.

Objective 4: To determine demographic, health-related, treatment, and physician-related factors are associated with the receipt the potentially interacting medications with statins.

Seven hypotheses were tested for Objective 4. A logistic regression model was used to test the hypotheses. The association between various demographic, health risk, treatment, and physician-related factors and odds of receiving a potentially interacting medication were assessed in a regression equation simultaneously. The regression coefficients obtained for the independent variables were logits which were converted to odds by exponentiation of the logits. The logistic model for the odds of receiving a potentially interacting medication i.e. Y = 1 for an any given subject i was

$$Yi = \frac{\exp(g(xi))}{1 + \exp(g(xi))}$$

Where g(xi) is the usual linear equation:

$$g(xi) = \beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k$$

With constant β_0, coefficients β_j, and predictors X_j for k predictors (j = 1, 2, 3 … k).[360] In this study the predictors to be included were age, gender, ethnicity/race, number of comorbidities, type and dose of statin, and physician specialty.

[360] Tabachnick BG, Fidell LS. Logistic Regression. In: Tabachnick BG, Fidell LS, eds. Using Multivariate Statistics. Boston: Allyn & Bacon, 2001:517-581.

Evaluation of incidence and the risk of myopathy in patients using statins with and without potentially interacting medications

Objective 5: To estimate the overall incidence of myopathy in the study population.

Descriptive analysis was used to evaluate the overall incidence (incidence density) of myopathy among Medicaid patients. As mentioned earlier (in the timeframe of the study section), incidence density takes into account different follow-up times for each patient. The formula to calculate incidence density is as follows:[361]

$$\text{Incidence density} = \frac{\text{New myopathy events over observation period}}{\text{Time spent by the study population at risk during observation period (person-months)}}$$

Or

$$= \frac{\text{Myopathy occurrences}}{\text{Sum of time periods}}$$

Myopathy incidence was calculated separately for the statin user and statin interacter groups. After the incidences were obtained, chi-square analysis was conducted for comparing the incident cases of myopathy between the two groups.

[361] Bhopal R. The concept of risk and measures of disease frequency. In: Bhopal R, ed. Concepts of Epidemiology: An integrated introduction to the ideas, theories, principles and methods of epidemiology. New York: Oxford University Press Inc., 2002:163-190.

Objective 6: To describe the demographic characteristics of the study population based on presence or absence of myopathy.

Frequencies, means, and standard deviations were used to address Objective 6. The patients were classified based on presence or absence of myopathy, and descriptive statistics were provided for each group separately.

Objective 7: To describe the "time to occurrence of myopathy" in patients receiving statins and potentially interacting medications, and patients receiving statins without potentially interacting medications.

Survival analysis was utilized to address Objective 7. Specifically, Kaplan-Meier analysis was used to estimate time to development of myopathy. Kaplan-Meier survival curves describe the length of time it takes for an event to occur in context of incomplete (censored) information. Using the Kaplan-Meier method, the time to myopathy was estimated and graphically described from the cumulative probability of surviving each of the time intervals that preceded development of myopathy. Statin users were compared with statin interacters on time taken to develop myopathy.

Objective 8: To assess the relationship between the development of myopathy and use of potentially interacting medications with statins, while controlling for other risk factors for myopathy.

Logistic regression was used to address Objective 8. There was one hypothesis

associated with this objective. Receipt of PIM was the independent variable. All the othe independent variables were controlled for in the model.

Objective 9: To determine the risk factors (demographic factors, comorbidity factors, treatment factors and physician-related factors) for myopathy.

There were 13 hypotheses that were tested in Objective 9. Two models were analyzed to answer Objective 9, as mentioned earlier. In Model 1, the statin interacter group was compared with the statin user group. In Model 2, only the statin interacter group was analyzed to determine PIM characteristics associated with risk of myopathy. Both models were analyzed using logistic regression. The regression coefficients were logits, and were exponentiated to obtain odds. Thus, the regression coefficient was interpreted as "odds of developing myopathy." The risk factors to be analyzed included age, gender, ethnicity/race, diabetes, number of comorbidities, receipt of potentially interacting medication, type and dose of statin, duration of statin use, level of significance of drug interaction, time and duration of use of potentially interacting medication, and physician specialty.

In summary, 22 hypotheses were tested in this study. The specific statistical tests for each of these hypotheses are shown in Table 2.10.

Table 2.10: Study hypotheses with proposed statistical tests

Study Hypothesis	Description	Statistical Tests
Evaluation of factors that are associated with the receipt of potentially interacting medication		
H_o1	There will be no difference in the odds of receipt of potentially interacting medication based on type of statin, while controlling for other factors.	Logistic Regression
H_o2	There will be no difference in the odds of receipt of potentially interacting medication based on dose of statin, while controlling for other factors.	Logistic Regression
H3	The odds of receipt of potentially interacting medication will increase with increasing age, while controlling for other factors.	Logistic regression
H_o4	There will be no difference in the odds of receipt of potentially interacting medication based on gender, while controlling for other factors.	Logistic Regression
H6	The odds of receipt of potentially interacting medication will increase with increasing number of comorbidities, while controlling for other factors.	Logistic Regression
H_o7	There will be no difference in the odds of receipt of potentially interacting medication based on physician specialty, while controlling for other factors.	Logistic Regression
Evaluation of risk factors that are associated with the development of myopathy		
H8	The odds of developing myopathy will be higher for statin interacters than for statin users, while controlling for other factors	Model 1: Logistic Regression
H9	The odds of developing of myopathy will increase with increasing age, while controlling for other factors.	Model 1: Logistic Regression

Table 2.10: Study hypotheses with proposed statistical tests (Continued)

Study Hypothesis	Description	Statistical Tests
H10	The odds of developing myopathy will be higher for females than males, while controlling for other factors.	Model 1: Logistic Regression
H_o11	There will be no difference in the odds of developing myopathy based on ethnicity/race, while controlling for other factors.	Model 1: Logistic Regression
H12	The odds of developing myopathy will be higher for patients with diabetes than those without diabetes, while controlling for other factors.	Model 1: Logistic Regression
H13	The odds of developing myopathy will increase with increasing number of comorbidities, while controlling for other factors.	Model 1: Logistic Regression
H14	The odds of developing myopathy will be higher for patients using simvastatin as compared to pravastatin, while controlling for other factors.	Model 1: Logistic Regression
H15	The odds of developing myopathy will be higher for patients using atorvastatin as compared to pravastatin, while controlling for other factors.	Model 1: Logistic Regression
H16	The odds of developing myopathy will be higher for patients using fluvastatin/lovastatin as compared to pravastatin, while controlling for other factors.	Model 1: Logistic Regression
H17	The odds of developing myopathy will be higher for patients on higher doses of statins than lower doses of statins, while controlling for other factors.	Model 1: Logistic Regression
H18	The odds of developing myopathy will increase with increasing duration of statin use, while controlling for other factors.	Model 1: Logistic Regression

Table 2.10: Study hypotheses with proposed statistical tests (Continued)

Study Hypotheses	Description	Statistical Tests
H19	The odds of developing myopathy will increase with increasing level of significance of drug interaction, while controlling for other factors.	Model 2: Logistic Regression
H_o20	There will be no difference in the odds of developing myopathy based on whether the potentially interacting medication was given at the start of statin therapy or on a later date, while controlling for other factors.	Model 2: Logistic Regression
H21	The odds of developing myopathy will increase with increasing duration of PIM use, while controlling for other factors.	Model 2: Logistic Regression
H_o22	There will be no difference in odds of developing myopathy based on physician specialty, while controlling for other factors.	Model 1: Logistic Regression

CHAPTER 3

RESULTS

This chapter presents the results of this study. First, the sample size is discussed after implementation of inclusion/exclusion criteria. This is followed by descriptive analysis of the variables included in the study, and finally the results for each objective are presented. The results of the objective analyses are presented in the order of objectives listed in Section VI of Chapter 1.

PATIENT SELECTION CRITERIA AND SAMPLE SIZE

The study population was followed from March 1, 1999 to August 31, 2003 as depicted in Figure 2.1 of Chapter 2. The study sample consisted of 8,822 patients who were enrolled in Texas Medicaid and were eligible for this study. Of these, 5,817 patients were statin users who never received potentially interacting medications (PIMs) during the observation period. The remaining 3,005 patients were statin users who received a potentially interacting medication.

Patient inclusion/exclusion criteria for the study were: 1) continuous enrollment for one year; 2) new statin user; 3) no diagnosis of myopathy six months before the start of statin therapy and three months before the index date; 4) no diagnosis of renal insufficiency, hepatic dysfunction or hypothyroidism throughout the study period; 5) no

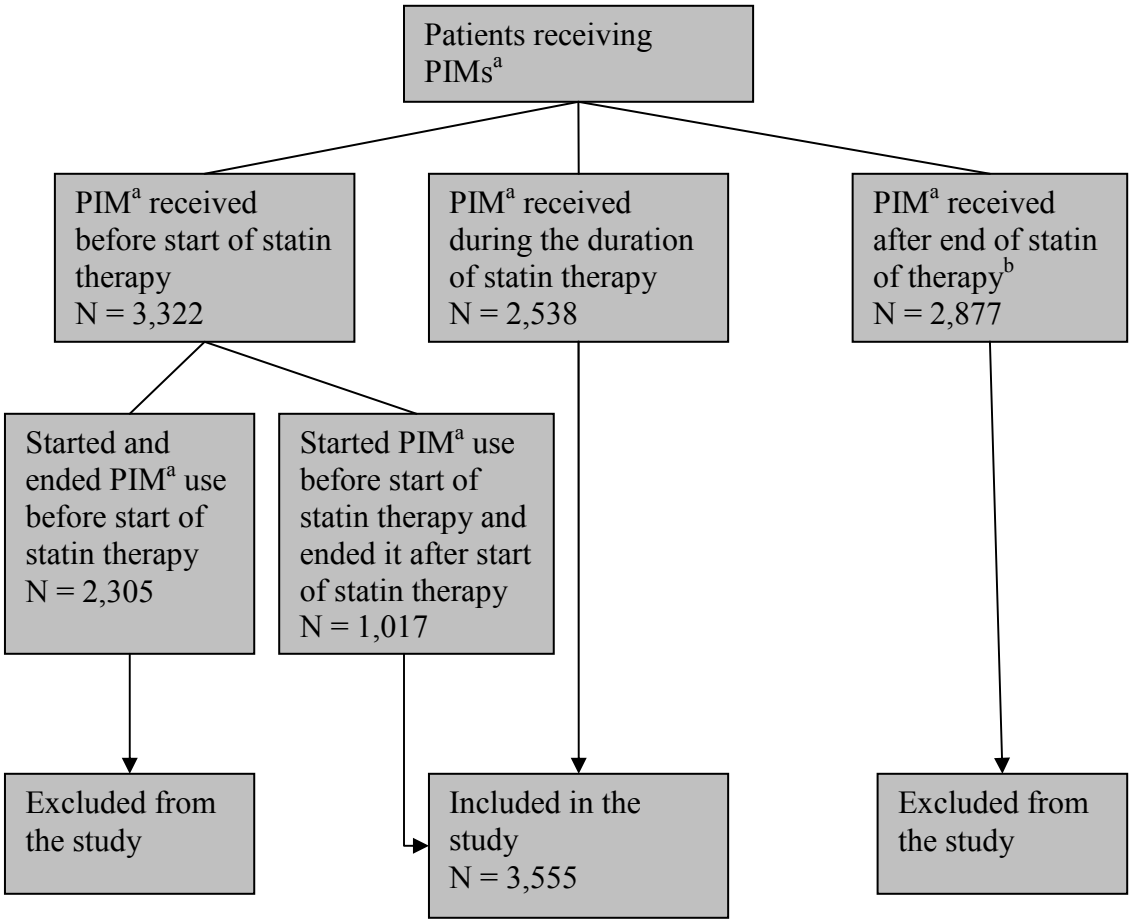
diagnosis of HIV throughout the study period; 6) no use of cerivastatin throughout the study period; 7) no switch in dose or type of statins throughout the study period, 8) age between 21 and 64 years; 8) did not receive PIMs during the duration of statin use (Figure 3.1), and 9) no switch in PIM use. Table 3.1 shows the patient inclusion criteria with the corresponding sample size after implementation of each criterion.

Table 3.1: Patient inclusion criteria and sample size

Patient Inclusion Criteria	Exclusion Number	Sample Size
1.Patients using statins		48,320
2. New statin user and continuous enrollment[a]	14,353	33,967
3. No prior myopathy event[b]	985	32,982
4. No diagnosis of renal insufficiency, hepatic dysfunction or hypothyroidism[c]	7,794	25,188
5. No HIV diagnosis[c]	409	24,779
6. No cerivastatin use[c]	966	23,813
7. No switch in dose and type of statins[c]	9,266	14,547
8. Age between 21 and 64 years	29	14,518
9. No receipt of PIMs[d] concurrently with statins	5,182	9,336
10. No switch in PIM[d] use	514	8,822

a. At least six months continuous enrollment before and after start of statin therapy
b. Six months prior to start of statin therapy and three months before index date
c. Throughout the study period
d. PIM – potentially interacting medication

Figure 3.1: Inclusion and exclusion number of patients receiving PIMs[a]



a. PIM- Potentially interacting medication
b. End of statin therapy is when there is a gap of greater than 45 days between two refills

DESCRIPTIVE STATISTICS

The risk factors that affect the study outcomes are shown in Figure 2.3 and Figure 2.4 in Chapter 2. These factors include demographic factors (age, gender, and race), health risk factors (presence of diabetes and number of comorbid conditions), treatment factors which include PIM characteristics (receipt of PIM, level of significance of interaction, and time/duration of PIM treatment) and statin characteristics (type and dose

of statin, and duration of statin use), and finally physician-related factors (physician specialty). Descriptive statistics are provided for each of the above-mentioned variables in the following section.

Demographic factors

Objective 3 was related to description of demographic characteristics of study population. This section describes in detail the characteristics of the patient population. Data is presented based on whether or not patients received PIMs.

Table 3.2 shows the gender distribution for statin user and statin interacter groups. A total of 5,193 patients were females (58.9%). The statin interacter group had a higher percent of females (65.3%, N = 1,961) than the statin user group (55.6%, N = 3,232). There was a statistically significant difference in gender distribution between the statin user and statin interacter groups ($\chi^2 = 76.93$; d.f. = 1; $p < 0.0001$).

Table 3.2: Frequency and percent of statin users and statin interacters by gender

Gender	Statin Users N (%)	Statin Interacters N (%)	Total N (%)
Females	3,232 (55.6)	1,961 (65.3)	5,193 (58.9)
Males	2,585 (44.4)	1,044 (34.7)	3,629 (41.1)
Total	5,817 (100.0)	3,005 (100.0)	8,822 (100.0)

$\chi^2 = 76.93$; d.f. = 1; $p < 0.0001$

Table 3.3 presents the ethnic/race distribution for the statin user and statin interacter groups. A total of 3,386 (38.4%) of the sample were Whites, 2,148 (36.9%) were in the statin user group and 1,238 (41.2%) were in the statin interacter group. Statin user group had more percent of Hispanics (N = 1,948, 33.6%) than statin interacter group (N = 818, 27.2%). There was a statistically significant difference between two groups based on ethnicity/race (χ^2 =38.09; d.f. = 5; p <0.0001).

Table 3.3: Frequency and percent of statin users and statin interacters by ethnicity/race

Ethnicity/Race	Statin Users N (%)	Statin Interacters N (%)	Total N (%)
White	2,148 (36.9)	1,238 (41.2)	3,386 (38.4)
Black	1,266 (21.8)	681 (22.7)	1,947 (22.1)
Hispanic	1,948 (33.5)	818 (27.2)	2,766 (31.3)
Native Indian	24 (0.4)	16 (0.5)	40 (0.5)
Asian	125 (2.2)	71 (2.4)	196 (2.2)
Other[a]	306 (5.3)	181 (6.0)	487 (5.5)
Total	5,817 (100.0)	3,005 (100.0)	8,822 (100.0)

χ^2 =38.09; d.f. = 5; p <0.0001

[a.] Other includes all other ethnicities except those mentioned above

The mean age for statin user group was 51.1 years (Standard Deviation (S.D.) = 9.9 years) while the mean age for statin interacter group was 51.4 years (S.D. = 9.7 years). There was no statistical difference in age between groups (t-value = -1.26; p = 0.20). Table 3.4 gives the frequency and percent of patients for statin users and statin

interacters by age groups. Patients aged 51 to 60 years represented 41.8% (N = 3,690) of the eligible population. The next largest group was comprised of patients aged between 41 and 50 years accounting for 24.1% (N = 2,123) of the eligible population.

Table 3.4: Frequency and percent of statin users and statin interacter by age groups

Age Group	Statin Users N (%)	Statin Interacters N (%)	Total N (%)
21-30	275 (4.7)	113 (3.8)	388 (4.4)
31-40	659 (11.3)	341 (11.3)	1,000 (11.3)
41-50	1,380 (23.7)	743 (24.7)	2,123 (24.1)
51-60	2,434 (41.9)	1,256 (41.8)	3,690 (41.8)
61-64	1,069 (18.4)	552 (18.4)	1,621 (18.4)
Total	5,817 (100.0)	3,005 (100.0)	8,822 (100.0)

Table 3.5 provides information on frequency and percent of statin users and statin interacters by gender and age groups. The statin user group had greater percent of males (6.0%) in the 21-30 age groups than statin interacter group (3.8%). Furthermore, there were a greater proportion of females in the older age categories. Overall, a χ^2 analysis revealed that there was a statistically significant difference between age groups for males and females for the statin user group ($\chi^2 = 88.29$; d.f. = 4; $p < 0.0001$). However, there was no such difference for the statin interacter group ($\chi^2 = 4.59$; d.f. = 4; $p = 0.33$).

Table 3.5: Frequency and percent of statin users and statin interacters by age groups and gender

Age Group	Statin Users		Statin Interacters	
	Females N (%)	Males N (%)	Females N (%)	Males N (%)
21-30	120 (3.7)	155 (6.0)	73 (3.7)	40 (3.8)
31-40	304 (9.4)	355 (13.7)	207 (10.6)	134 (12.8)
41-50	697 (21.6)	683 (26.4)	479 (24.4)	264 (25.4)
51-60	1,443 (44.7)	991 (38.3)	833 (42.5)	423 (40.5)
61-64	668 (20.6)	401 (15.6)	369 (18.8)	183 (17.5)
Total	3,232 (100.0)	2,585 (100.0)	1,961 (100.0)	1,044 (100.0)
	$\chi^2 = 88.29$; d.f. = 4; $p < 0.0001$		$\chi^2 = 4.59$; d.f. = 4; $p = 0.33$	

Health risk factors

The two health risk factors that were included in the study were presence of diabetes and number of comorbidities.

Diabetes

A total of 4,272 (48.4%) patients had a diagnosis of diabetes as identified by ICD-9-CM codes or use of anti-diabetes drugs. A little more than half the patients (N = 4,550, 51.6%) had no diagnosis for diabetes. When broken down by cohorts, statin interacters had a higher percentage of diabetes patients (N = 1,550, 51.6%) than statin users (N = 2,722, 46.8%).

Number of comorbidities

The major clinical conditions and ICD-9-CM codes used to define comorbidities are as shown in Table 2.6 in Chapter 2. Table 3.5 shows the number and percent of statin users and statin interacters by number of comorbidities. A total of 3,630 (41.1%) patients had at least one comorbidity. The remaining 5,192 (58.9%) patients had no comorbidities. The statin interacter group had significantly (χ^2 =198.58; d.f. = 5; p <0.0001) higher percentage of patients with comorbidities (N = 1,507; 40.1%) than statin user group (N = 2,123; 36.5%).

Table 3.5: Frequency and percent of statin users and statin interacters by number of comorbidities

Number of Comorbidities	Statin Users N (%)	Statin Interacters N (%)	Total N (%)
0	3,694 (63.5)	1,498 (49.9)	5,192 (58.9)
1-2	1,966 (33.8)	1,325 (44.1)	2,375 (26.9)
3-4	149 (2.6)	169 (5.6)	318 (36.0)
> 5	8 (0.1)	13 (0.4)	21 (0.2)
Total	5,817 (100.0)	3,005 (100.0)	8,822 (100.0)

χ^2 =198.58; d.f. = 5; p <0.0001

Treatment factors

The treatment factors that were included in this study were characteristics of statin used and characteristics of PIM used by the eligible patients. The next section describes these variables in detail.

Statin characteristics

Objective 1 was related to providing descriptive statistics on type and dose of statins. Table 3.6 presents information on frequency and percent of type and dose of statin prescribed to patients for the first time. Patients used atorvastatin (N = 4,894; 55.5%) most frequently, followed by simvastatin (N = 2,219; 25.2%), pravastatin (N = 1,159; 13.1%), fluvastatin (N = 465; 5.3%) and lovastatin (N = 85; 0.9%).

Table 3.6: Frequency and percent of patients based on statin type and dose prescribed for first time

Statin Type and dose	Number of patients (%)	Percent of total patients
Atorvastatin		
10mg	3,494 (71.4)	39.6%
20mg	1,083 (22.1)	12.3%
40mg	279 (5.7)	3.2%
80 mg	38 (0.8)	0.4%
Total	**4,894 (100.0)**	**55.5%**
Simvastatin		
5mg	19 (0.9)	0.2%
10mg	275 (12.4)	3.2%
20mg	1,144 (51.5)	13.0%
40 mg	630 (28.4)	7.1%
80 mg	151 (6.8)	1.7%
Total	**2,219 (100.0)**	**25.2%**
Pravastatin		
10mg	44 (3.8)	0.5%
20mg	623 (53.8)	7.1%
40mg	482 (41.6)	5.4%
80mg	10 (0.9)	0.1%
Total	**1,159 (100.0)**	**13.1%**
Fluvastatin		
20mg	156 (33.6)	1.8%
40mg	181 (38.9)	2.0%
80mg	128 (27.5)	1.5%
Total	**465 (100.0)**	**5.3%**
Lovastatin		
10mg	19 (22.3)	0.2%
20mg	43 (50.6)	0.5%
40mg	15 (17.7)	0.1%
60mg	8 (9.4)	0.1%
Total	**85 (100.0)**	**0.9%**
Total	**8,822**	**100.0%**

As seen from the Table 3.6, most patients (N = 7,066; 80.1%) were started on low doses of statins, as recommended by package inserts of these statins. A total of 3,494 patients (40%) were started on 10mg of atorvastatin and 1,144 (13%) patients were started on 20mg of simvastatin. Based on categorization of doses (as shown in Table 2.7 of Chapter 2) where Group I consists of lower doses of statins and group II consists of higher doses of statins, a total of 6,601 patients (74.8%) were started on lower doses of statin and 2,221 (25.2%) patients were started on high doses of statins.

Table 3.7 shows the frequency and percent of statin users and statin interacters by statin type used for the first time. Table 3.8 shows the frequency and percent of statin users and statin interacters by statin dose. Both cohorts were comparable in the type and dose of statin used. However, the statin interacter group had a slightly greater use of pravastatin (14. 2%) and higher percent of high dose fluvastatin users than the statin user group (12.6%).

Table 3.7: Frequency and percent of statin users and statin interacters by type of statin used

Statin type	**Statin Users N (%)**	**Statin Interacters N (%)**
Atorvastatin	3,220 (55.3)	1,674 (55.7)
Simvastatin	1,483 (25.5)	736 (24.5)
Pravastatin	732 (12.6)	427 (14.2)
Fluvastatin	319 (5.5)	146 (4.9)
Lovastatin	63 (1.1)	22 (0.7)
Total	**5,817 (100.0)**	**3,005 (100.0)**

χ^2 =8.8; d.f. = 5; p = 0.06

Table 3.8: Frequency and percent of statin users and statin interacters by dose of statin

Statin type and dose	Statin Users N (%)	Statin Interacters N (%)
Atorvastatin		
10mg	2,299 (71.4)	1,195 (71.4)
20mg	724 (22.5)	359 (21.4)
40mg	174 (5.4)	105 (6.3)
80 mg	23 (0.7)	15 (0.9)
Total	**3,220 (100.0)**	**1,674 (100.0)**
	χ^2 =2.46; d.f. = 3; p = 0.48	
Simvastatin		
5mg	16 (1.1)	3 (0.4)
10mg	188 (12.7)	87 (11.9)
20mg	757 (51.1)	387 (52.6)
40 mg	415 (27.9)	215 (29.2)
80 mg	107 (7.2)	44 (5.9)
Total	**1,483 (100.0)**	**736 (100.0)**
	χ^2 =4.47; d.f. = 4; p = 0.34	
Pravastatin		
10mg	24 (3.3)	20 (4.7)
20mg	389 (53.1)	234 (54.8)
40mg	312 (42.7)	170 (39.8)
80mg	7 (0.9)	3 (0.7)
Total	**732 (100.0)**	**427 (100.0)**
	χ^2 =2.25; d.f. = 3; p = 0.52	
Fluvastatin		
20mg	119 (37.3)	37 (25.3)
40mg	114 (35.8)	67 (45.9)
80mg	86 (26.9)	42 (28.8)
Total	**319 (100.0)**	**146 (100.0)**
	χ^2 =7.04; d.f. = 2; p = 0.02	
Lovastatin		
10mg	16 (25.4)	3 (13.6)
20mg	30 (47.6)	13 (59.1)
40mg	11 (17.5)	4 (18.2)
60mg	6 (9.5)	2 (9.1)
Total	**63 (100.0)**	**22 (100.0)**
	Not applicable[a]	

[a.] 38% of the cells have expected counts less than 5

Duration of statin treatment was defined as the time period a patient is exposed to statin treatment before the end of observation period. The end of observation period occurs when any one of the following three criteria are met: 1) diagnosis of myopathy; 2) discontinued statin therapy (a gap of greater than 45 days between refills); or 3) end of six month follow-up period. The time period was then calculated as sum of days' supply between the first and last prescription. Based on these criteria, the average duration of statin use was 154 days (S.D. = 137 days) with a minimum use of one day and a maximum use of 1,661 days. When both cohorts were compared, the duration of statin use was statistically greater for statin interacters than for statin users (t-value = -26.77; $p<0.0001$) (Table 3.9).

Table 3.9: Mean, standard deviation, minimum, and maximum duration of statin use (no gap greater than 45 days between refills) for statin users and statin interacters

Duration of Statin Use (Days)	**Statin Users N = 5,817**	**Statin Interacters N = 3,005**
Mean	120	221
Standard Deviation	62	202
Minimum	3	1
Maximum	180	1661
t-value = -26.77; $p < 0.0001$		

Table 3.10 provides descriptive statistics on duration of statin use for statin users and statin interacters with 60-day gap between refills was used. When this criterion for

discontinuation of statin was changed, a total of 8,911 patients were included in study, the details of which are discussed in Appendix D. Based on this criterion, the average duration of statin use was 164 days (S.D. = 146 days) with a minimum of 1 day and maximum of 1661 days. There was a statistically significant difference in the duration of statin use between statin interacters and statin users (t-value = -28.73; p<0.0001).

Table 3.10: Mean, standard deviation, minimum, and maximum duration of statin use (no gap greater than 60 days between refills) for statin users and statin interacters

Duration of Statin Use (Days)	**Statin Users N = 5,817**	**Statin Interacters N = 3,094**
Mean	125	238
Standard Deviation	61	214
Minimum	3	1
Maximum	180	1661
t-value = -28.73; p < 0.0001		

PIM characteristics

A total of 3,005 patients received potentially interacting medications along with statin medications. These patients formed the statin interacter group. A total of 2,207 (73.4%) patients received PIMs after the start of statin therapy whereas a total of 798 (26.6%) patients were using PIMs before start of statin therapy.

Objective 2 aimed at providing descriptive statistics on type of potentially interacting medications. Table 3.11 shows the frequency and percent of patients by type of PIM used.

Table 3.11: Frequency and percent of patients using PIMs

Type of PIM	Frequency	Percent
Fibrates[a]	379	12.6%
Nicotinic Acid	65	2.2%
Antiarrthymic[b]	59	2.0%
Calcium Channel Blockers[c]	879	29.2%
Antidepressants[d]	90	2.9%
Macrolide Antibiotics[e]	1,225	40.8%
Azole Antifungals[f]	308	10.3%
Total	**3,005**	**100.0%**

a. Fibrates include gemfibrozil and fenofibrate
b. Antiarrthymics include amiodarone
c. Calcium Channel Blockers include diltiazem and verpamil
d. Antidepressants include nefazodone
e. Macrolide antibiotics include erythromycin, clarithromycin, and azithromycin
f. Azole Antifungals include fluconazole, ketoconazole and itraconazole

A total of 1,225 (40.8%) patients used macrolide antibiotics and a total of 308 (10.3%) patients used azole antifungals. These products are normally used for a short period. Among the remaining patients, calcium channel blockers (N = 879; 29.2%) and fibrates (N = 379; 12.6%) were the most often used potentially interacting medication.

Based on type of PIM used, the level of significance of drug interaction were characterized into following three levels: 1) Level 1 is defined as potentially severe or life threatening interaction; 2) Level 2 is defined as interaction that causes detoriation in patients' clinical status and; 3) Level 3 is defined as moderate to minor side effects. Table 3.12 provides information on frequency and percent of patients based on level of significance of drug interaction. A total of 1,694 patients (56.4%) were classified as receiving a PIM which was defined as severe or life-threatening.

Table 3.12: Frequency and percent of patients by level of drug interaction significance based on type of PIM[a] used

Level of Significance of Drug Interaction	Type of PIM[a]	Frequency	Percent
Level 1[b]	Fibrates, Antidepressants, Antibiotics	1,694	56.4%
Level 2[c]	Calcium Channel Blockers, Antifungals	1,187	39.5%
Level 3[d]	Nicotinic acid, amiodarone	124	4.1%
Total		3,005	100.0%

[a.] PIM – Potentially Interacting Medication
[b.] Level 1 is defined as a potentially severe or life threatening interaction.
[c.] Level 2 is defined as interaction that causes detoriation in patients' clinical status.
[d.] Level 3 is defined as moderate to minor side effects.

Duration of PIM use was defined as the number of days of PIM use before the end of the observation period. The end of the observation period occurs when any one of the following three criteria are met: 1) diagnosis of myopathy; 2) discontinued statin therapy

(a gap of greater than 45 days between refills) or PIM use; or 3) end of six month follow-up period. The average duration of PIM use was 58 days (S.D=67 days) with a minimum of one day and a maximum of 253 days. Table 3.13 provides descriptive statistics on duration of PIM use based on type of PIM. Calcium channel blockers had the highest mean number of days (121 days) whereas macrolide antibiotics had the shortest (8 days).

Table 3.13: Mean, standard deviation, minimum and maximum of duration of PIM use before end of observation period based on therapeutic class of PIM

Type of PIM	N	Mean (days)	Standard Deviation (days)	Minimum (days)	Maximum (days)
Fibrates	379	92	57	20	226
Nicotinic Acid	65	95	59	30	180
Antiarrthymic	59	111	66	9	200
Calcium Channel Blockers	879	121	60	9	253
Antidepressants	90	92	58	20	184
Macrolide Antibiotics	1,225	8	9	1	161
Azole Antifungals	308	12	23	1	150

Physician specialty

Information on the specialty of the prescribing physician at index date was obtained from Texas State Board of Medical Examiners (TSBME) database. The physician's unique license number was used to link the Medicaid file with the database obtained from TSBME. Overall, physician specialty was available for 7,519 patients

(85.2%) out of a total of 8,822 patients. A total of 3,450 prescriptions (45.9%) were written by family practice/general practice physicians. However, the statin user group had more patients (N = 2,331; 48.0%) whose prescription was written by family practice/general practice than the statin interacter group (N = 1,119; 42.1%) (Table 3.14). There was a statististically significant difference in physician specialty when comparing statin interacters with statin users (χ^2 =32.1; d.f. = 3; p <0.0001).

Table 3.14: Frequency and percent of patients by physician specialty who wrote statin prescription at index date

Physician Specialty	Statin Users N (%)	Statin Interacters N (%)	Total N (%)
Family practice/ General practice	2,331 (48.0)	1,119 (42.1)	3,450 (45.9)
Internal Medicine	1,479 (30.4)	841 (31.7)	2,320 (30.8)
Cardiologists	328 (6.7)	189 (7.1)	517 (6.9)
Other[a]	725 (14.9)	507 (19.1)	1,232 (16.4)
Total[b]	4,863 (100.0)	2,656 (100.0)	7,519 (100.0)

χ^2 =32.1; d.f. = 3; p <0.0001

[a.] Other category includes all physician specialties except those mentioned above.
[b.] Data on physician specialty were missing for 1,303 patients.

ASSESSING BASELINE CHARACTERISTICS

The above section provided descriptive statistics for both cohorts on all variables involved in the study. In order to assess potential differences in baseline characteristics, the demographic, health risk, treatment and physician-related factors were compared

between statin users and statin interacters. For continuous variables namely age and duration of statin use t-tests were used. For categorical variables, chi-square was used to evaluate the differences between the groups.

The baseline characteristics of the two cohorts were different on some variables. There was no statistically significant difference in the age groups between the two groups. However, there were significantly more females (Table 3.2) and a greater percent of Whites (Table 3.3) in the statin interacter group than statin user group. The statin user group had a greater percent of Hispanics than the statin interacter group (Table 3.3).

The doses and type of statin used in both groups were similar (Tables 3.7 and 3.8). However, the duration of statin use was significantly higher in the statin interacter group than the statin user group. Also, the statin interacter group had significantly more proportion of patients with diabetes (51.6% vs. 46.8%) and higher proportion of comorbidities (40.1% vs. 36.4%) than the statin user group. Finally, the statin user group had significantly more percent of family practice/general practice physicians who had written prescriptions than the statin interacter group (Table 3.14).

In summary, there were differences in the characteristics of patients in the two cohorts. However, these differences in baseline characteristics were controlled for in the regression analyses to avoid distortion of findings.

DATA MANAGEMENT

Two major statistical tools were used in assessing the study objectives: Kaplan-Meier survival analysis and logistic regression analyses. The Kaplan-Meier technique was used for unadjusted description and graphical representation of survival data. Therefore, assumptions regarding the distribution of covariates and survival times were not required. There are assumptions that are related to logistic regression which are reviewed in the next section. First, the general data cleaning and assessment step are discussed.

Accuracy of data file and distribution of variables

Descriptive statistics of the study variables have been described in the previous section of the chapter. Frequencies were calculated for all variables to check for coding errors, outliers and distribution of variables. There were no coding errors for any of the variables of the study. Normality plots, means and standard deviations were calculated for continuous variables age, duration of statin use and duration of PIM use. Age was negatively skewed whereas duration of statin use and PIM use were positively skewed (Appendix E). However since logistic regression is used as method of analysis, which does not make assumptions about shape of predictors, deviation from normality was not likely to pose a problem.[362] Also, the sample size was large enough not to cause problems in the analysis.[363]

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[362] Tabachnick BG, Fidell LS. *Logistic Regression*. In: Tabachnick BG, Fidell LS, eds. Using Multivariate Statistics. Boston: Allyn & Bacon, 2001:517-581.

[363] Tabachnick BG, Fidell LS. *Cleaning up your act: Screening data prior to analysis*. In: Tabachnick BG, Fidell LS, eds. Using Multivariate Statistics. Boston: Allyn & Bacon, 2001:56-100.

Assessment of missing data

The data were complete for all variables except physician specialty. There were 1,303 (14.8%) missing values for physician specialty. It has been suggested that the pattern of missing data is more important than the amount of missing data.[364] This is because data missing in a systematic manner may cause more problems in the analysis than missing data scattered across dataset. Missing data were scattered across dataset; however, since a large percent of values are missing for physician specialty this variable was excluded from the main analyses.

Assumptions of logistic regression analysis

Although logistic regression makes no assumptions about the distribution of independent variables, assumptions such as sampling adequacy, linearity among predictors, absence of multicollinearity and outliers, and independence of errors are critical to logistic regression.[365] All observations were mutually exclusive. Therefore, the assumption of independence of errors was not violated. All other assumptions were tested as part of the analysis for all logistic regression models and the results are presented in Appendix F.

[364] Ibid.
[365] Tabachnick BG, Fidell LS. *Logistic Regression*. In: Tabachnick BG, Fidell LS, eds. Using Multivariate Statistics. Boston: Allyn & Bacon, 2001:517-581.

Adequacy of expected frequencies and power

A goodness-of-fit test compares observed frequencies with expected frequencies formed by combinations of discrete variables. If the expected frequencies are too small, the analysis may lack power. Therefore, it is important to evaluate the expected cell frequencies for all variables including outcome variables. The requirement of sampling adequacy is that no more than 20% of cells should have expected frequency less than 5 and no cell should have expected frequency less than one.[366]

This assumption was violated in two of the three logistic regression models. In logistic regression models, evaluating the odds of developing myopathy, the expected call count for ethnicity Asian was less than one. Hosmer and Lemeshow[367] recommend collapsing the categories in order to increase the cell size of expected frequencies. Based on this recommendation, the category for Asian ethnicity was collapsed with the category for "Other" ethnicities. Also, 25% of cells had expected frequency less than 5 for lovastatin and fluvastatin users. Therefore, these two categories were collapsed to form a new category called "other statins".

Linearity among predictors

Although there are no assumptions about linear relationships among predictor variables themselves in logistic regression, there is an assumption of linearity between continuous predictor variables and the logit transformation of the outcome variable. This

[366] Ibid.
[367] Hosmer DW, Lemeshow S. *Assessing the fit of the model*. In: Hosmer DW, Lemeshow S, eds. Applied Logistic Regression. New York: John Wiley & Sons, 1989:135-173.

linearity assumption between predictor variables and the logit of dependent variable can be tested using Box-Tidwell approach.[368] In this approach, an interaction term of the continuous variable and its natural logarithm is added along with other variables to the logistic regression model. The assumption is violated if one or more of added interaction terms are statistically significant. The interaction terms were not statistically significant in any of the logistic regression models (Appendix F). Therefore, linearity in the logit assumption was not violated.

Assessment of multicollinearity

Logistic regression is sensitive to high correlations among predictor variables. If two predictor variables are highly correlated, the estimate of its effect on the dependent variable will be unstable. This will be indicated with high standard errors.[369] In order to assess multicollinearity you can evaluate standard errors but more formal testing is recommended. Therefore in addition to evaluating standard errors, bivariate correlations among all variables, and tolerance and variance inflation factor for each parameter estimate was also evaluated. Tolerance and variance inflation factor measure the inflation in the variances of the parameter estimates due to multicollinearities that exist among the variables. There are no formal cutoff values to indicate multicollinearity.

[368] Tabachnick BG, Fidell LS. *Logistic Regression*. In: Tabachnick BG, Fidell LS, eds. Using Multivariate Statistics. Boston: Allyn & Bacon, 2001:517-581.
[369] Allison PD. Logistic Regression: Using the SAS system - Theory and application. Cary: SAS Institute Inc. and John Wiley & Sons, 1999.

However, tolerances below 0.40 or variance inflation factor greater than 5.0 may indicate multicollinearity.[370]

The standard errors of parameter estimates in all the logistic regression models were low as shown in tables later. All of the bivariate correlations among explanatory variables were low. An examination of tolerance and variance inflation factor of parameter estimates revealed that none of the tolerance values were below 0.4 and none of variance inflation values were above five (Appendix F). All these tests indicate that there was no problem of multicollinearity in any of the logistic regression models.

Assessment of outliers

The presence of outliers is problematic as it may lead to Type I and Type II errors and the results may be only generalizable to populations with similar outlier characteristics. Frequency distributions were reviewed for each of the three continuous variables. Additionally, histograms for continuous variables were evaluated for each group. No outliers were detected from visual evaluation. Additionally, minimum and maximum standardized z-scores were calculated using the following formula[371]

$Z = (Y - Y`)/ SD$ where

Y = each variable's minimum or maximum value

Y` = mean of the variable

SD = standard deviation.

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[370] Ibid.

[371] Tabachnick BG, Fidell LS. *Cleaning up your act: Screening data prior to analysis*. In: Tabachnick BG, Fidell LS, eds. Using Multivariate Statistics. Boston: Allyn & Bacon, 2001:56-100.

Those cases with z-scores in excess of 3.3 were considered as outliers.[372] Based on these assessments age and duration of PIM use had no univariate outliers. However duration of statin use (Zmax = 10.99) had univariate outliers. Although the discrepancies were statistically significant, given the large sample size, they did not appear to be extreme. Therefore, no cases were deleted from the analyses.

Another way to assess the effect of outliers is to assess the goodness-of-fit indices. The chi-square statistic is the sum of Pearson's residuals.[373] Therefore if the model shows an adequate fit there is no need to search for outliers. All of the logistic regression models showed adequate fit. These fits are discussed later in detail in objective analyses. Therefore, outliers are not an issue in any of the models.

ANALYSES OF STUDY OBJECTIVES

There were nine objectives in this study addressing two main goals:

1) Evaluation of trends in prescribing patterns of potentially interacting medications with statins and;
2) Evaluation of incidence and risk factors of myopathy in patients receiving statins with and without potentially interacting medications.

There were four objectives addressing the first goal, and five objectives addressing the second goal of the study. Objectives one to three addressing the first goal of the study were exploratory in nature with no corresponding hypotheses. This has been

[372] Ibid.
[373] Tate R. An introduction to modeling outcomes in the behavioral and social sciences. Edina, MN: Burgess International Group, Inc., 1998.

discussed in detail under demographic factors, statin characteristics and PIM characteristics. A summary of these objectives is presentedin the following section. Objective four, which was aimed at identifying factors that are associated with receipt of PIMs with statins, had seven hypotheses. Logistic regression was used to address objective four. The second goal of the study had five objectives of which the first three were exploratory in nature. Survival analysis was used to address objective seven. The remaining two objectives that assessed the relationship between myopathy and receipt of PIMs with statins as well as association between myopathy and risk factors had 15 hypotheses associated with it. Logistic regression was used to address objectives eight and nine.

The independent variables in the logistic regression were either continuous variables or categorical variables. Some of the categorical variables such as ethnicity, level of significance of drug interaction, and type of statin had more than two categories. These variables had to be dummy coded to convert them into a set of dichotomous variables with categories being one less than total number of discrete categories. The variable physician specialty was excluded from the analysis due to missing data. Therefore, hypotheses related to this variable could not be tested. In total, 21 hypotheses were tested. The variables were entered simultaneously in the regression analysis.

The model fit of logistic regression models was assessed using global chi-square test and the Hosmer and Lemeshow statistic. The global chi-square statistic tests the null hypothesis that is there is no difference between a model with no predictors (constant-

only model) and a model with predictors (constant + predictors).[374] A significant chi-square ($p < 0.05$) indicates rejection of the null (i.e., there is a difference between the two models) and thus, there is an acceptable model fit.

The Hosmer and Lemeshow statistic calculates predicted probabilities, divides them into approximately 10 intervals and then computes a chi-square statistic based on observed and expected frequencies within those intervals. The Hosmer and Lemeshow statistic tests the null hypothesis that there is no difference between observed and predicted frequencies over the 10 intervals for a model that fits the data well. A non-significant chi-square ($p > 0.05$) indicates that the null hypothesis is not rejected supporting the assumption of correct model fit.[375]

Goal 1: Evaluation of trends in prescribing patterns of potentially interacting medications with statins

Objectives one to four corresponded to the above-mentioned goal. A summary of objectives one to three is presented here. These objectives have been discussed in detail in the descriptive section of this chapter.

Summary of objectives 1 to 3

Objective 1 aimed to provide descriptive statistics on type and dose of statin used. The most commonly used statins by patients was atorvastatin (N = 4,894; 55.5%),

[374] Tabachnick BG, Fidell LS. *Logistic Regression*. In: Tabachnick BG, Fidell LS, eds. Using Multivariate Statistics. Boston: Allyn & Bacon, 2001:517-581.
[375] Tate R. An introduction to modeling outcomes in the behavioral and social sciences. Edina, MN: Burgess International Group, Inc., 1998.

followed by simvastatin (N = 2,219; 25.2%), pravastatin (N = 1,159; 13.1%), fluvastatin (N = 465; 5.3%) and lovastatin (N = 85; 0.9%). A total of 7,066 patients (80.1%) were started on low doses of statins, as recommended by package inserts of these statins. Of these, 3,494 (40%) patients were started on 10mg of atorvastatin and 1,144 (13%) patients were started on 20mg of simvastatin.

Objective 2 addressed the frequency and percent of the type of potentially interacting medication. A total of 3,005 patients used potentially interacting medications. The most frequently used PIM was macrolide antibiotics (N = 1,225; 4.0.8%), followed by calcium channel blockers (N = 879; 29.2%) and fibrates (N = 379; 12.6%).

Objective 3 aimed to describe demographic characteristics of study population based on whether or not they receive potentially interacting medications. Table 3.15 provides a summary of demographic characteristics of both cohorts.

Table 3.15: Percent, means and standard deviation of demographic characteristics by statin users and statin interacters

Variable	Statin Users	Statin Interacters
Age (years): Mean (SD)	51.1 (9.9)	51.4 (9.7)
Gender		
Females (%)	55.6	65.3
Males (%)	44.4	34.7
Ethnicity/Race		
Whites (%)	36.9	41.2
Blacks (%)	21.8	22.7
Hispanics (%)	33.6	27.2
Asians (%)	2.2	2.4
Others (%)	5.7	6.5

Objective 4: To identify demographic, health-related, treatment, and physician-related factors that are associated with the receipt of potentially interacting medications.

The association between the receipt of potentially interacting medications and various risk factors was evaluated using logistic regression. The physician specialty factor was not included in the analysis due to missing data. The logistic model for the odds of receiving a potentially interacting medication (i.e., Y = 1) for any given subject i is

$$Yi = \frac{\exp(g(xi))}{1 + \exp(g(xi))}$$

Where g(xi) is the usual linear equation:

$$g(xi) = \beta_0 + \beta_1 X_1 + \ldots\ldots + \beta_k X_k$$

With constant β_0, coefficients β_j, and predictors X_j for k predictors (j = 1, 2, 3 … k).

The logistic regression model showed an improvement in fit based on the global chi-square test ($\chi^2 = 312.5$; df = 12; $p < 0.05$) and an acceptable functional form based on the Hosmer and Lemeshow statistic ($\chi^2 = 5.1$; df = 8; $p > 0.05$). The results of the regression analyses are shown in Table 3.16.

Table 3.16: Logistic regression analyses to identify risk factors associated with odds of receiving a potentially interacting medication

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value	Odds Ratio	95% Confidence Interval for Odds Ratio	
							Lower	Upper
Age	-0.005	0.002	5.000	1	0.025*	0.995	0.990	0.999
Gender (Female)[a]	0.429	0.048	81.084	1	<0.0001*	1.536	1.399	1.686
Ethnicity (Black)[b]	-0.080	0.061	1.731	1	0.188	0.923	0.819	1.040
Ethnicity (Hispanic)[b]	-0.281	0.055	25.326	1	<0.001*	0.755	0.676	0.842
Ethnicity (Asian)[b]	0.094	0.155	0.367	1	0.544	1.099	0.810	1.490
Ethnicity (Other)[b]	0.012	0.099	0.015	1	0.901	1.012	0.834	1.229
Comorbidities	0.355	0.026	183.334	1	<0.001*	1.427	1.355	1.502
Fluvastatin[c]	-0.221	0.119	3.450	1	0.063	0.801	0.634	1.012
Atorvastatin[c]	-0.113	0.070	2.562	1	0.109	0.893	0.777	1.026
Lovastatin[c]	-0.494	0.258	3.653	1	0.055	0.610	0.367	1.013
Simvastatin[c]	-0.183	0.079	5.328	1	0.021*	0.832	0.712	0.973
Dose of statin[d]	-0.033	0.055	0.372	1	0.541	0.967	0.867	1.078

* $p<0.05$
[a.] Reference category is male
[b.] Reference category is Whites
[c.] Reference category is pravastatin
[d.] Reference category is low dose of statin

Among all the risk factors that were evaluated, increasing age, being Hispanic, and receiving simvastatin had lower odds of receiving potentially interacting medication. Being female and having a greater number of comorbidities had higher odds of receiving potentially interacting medications. The odds of receipt of PIM was greatest for females (Odds ratio (OR): 1.536; 95% CI: 1.399-1.686) and those with increasing number of

comorbidities (OR: 1.427; 95% CI: 1.355-1.502). Based on the results of the analyses, hypotheses one to seven are presented in following section.

Results of hypotheses tests

Hypothesis 1: There will be no difference in the odds of receipt of potentially interacting medication based on type of statin, while controlling for other factors.

Based on the results of the logistic regression (Table 3.16), patients on simvastatin had significantly lower odds (OR: 0.832; 95% CI: 0.712-0.973) of receiving PIMs than patients on pravastatin. However, there was no difference in the odds of receiving PIMs for the remaining categories of statins. Thus, hypothesis 1 was rejected.

Hypothesis 2: There will be no difference in the odds of receipt of potentially interacting medication based on dose of statin, while controlling for other factors.

The doses of statins were categorized into two groups based on the comparative efficacy of the statins on lipid levels (Table 2.7 in Chapter 2). All the doses in group I are lower and have lower reduction in lipid levels as compared to doses of statins in group II . Based on the results shown in Table 3.16, hypothesis 2 was not rejected. There was no difference in odds of receiving PIM based on dose of statin (OR:0.967; 95% CI: 0.867-1.078), controlling for all other factors.

Hypothesis 3: *The odds of receipt of potentially interacting medication will increase with increasing age, while controlling for other factors.*

Based on the results of the regression analysis (Table 3.16), increasing age had lower odds of receiving a PIM (OR: 0.995; 95% CI: 0.990-0.999), controlling for all other factors. The odds ratio is so close to one that even though the results are statistically significant, the difference between two groups is minimal. Nevertheless, hypothesis 3 is rejected.

Hypothesis 4: There will be no difference in the odds of receipt of potentially interacting medication based on gender,while controlling for other factors.

Based on the results of the logistic regression (Table 3.16), hypothesis 4 was rejected. Females had a 53.6% (OR: 1.536; 95% CI: 1.399-1.686) higher odds of receiving PIM than males, controlling for all other factors.

Hypothesis 5: There will be no difference in the odds of receipt of potentially interacting medication based on ethnicity/race, while controlling for other factors.

Based on the results of the logistic regression presented in Table 3.16, being Hispanic had statistically significant lower odds (OR:0.755; 95% CI: 0.676-0.842) of receiving a PIM as compared to Whites. Blacks had lower odds whereas Asians and other ethnicities had higher odds of receiving PIM than Whites, but the results were not statistically significant. Based on these results, hypothesis 5 was rejected.

Hypothesis 6: The odds of receipt of potentially interacting medication will increase with increasing number of comorbidities, while controlling for other factors.

The odds of receipt of potentially interacting medication increased 42% (OR: 1.427; 95% CI: 1.355-1.502) with increasing number of comorbidities, controlling for all other factors. Based on these results, hypothesis 6 was not rejected.

Hypothesis 7: There will be no difference in the odds of receipt of potentially interacting medications based on physician specialty, while controlling for other factors.

It was not possible to test this hypothesis, as the physician specialty variable was not included in the analysis due to missing data.

Goal 2: Evaluation of incidence and risk factors for myopathy in patients receiving statins with and without potentially interacting medications

As mentioned earlier, objectives 5 to 9 corresponded to goal two. Objectives 5 to 7 were exploratory in nature. Descriptive statistics were used to answer objectives 5 to 7. Objectives 8 and 9 were assessed using logistic regression. A total of 15 hypotheses were associated with objectives 8 and 9. The results of each of the objective analyses are discussed in the following section.

Objective 5: To estimate the overall incidence of myopathy among study population.

The main outcome of this study was to determine the incidence of myopathy in the study population. The patients were followed from the index date until one of the following endpoints:

1) diagnosis of myopathy as identified by ICD-9-CM codes as discussed in methodology chapter;
2) discontinued statin therapy (a gap of 45 days or greater) or PIM use; or
3) end of the six-month follow-up from the index date.

Follow-up times were calculated in terms of person-months where person-month was duration of time between index date and one of the above-mentioned endpoints. The cumulative incidence rate or incidence density was then calculated using following formula:

$$\text{Incidence density} = \frac{\text{Myopathy Occurrences}}{\text{Sum of time periods}} \times 100$$

A total of 113 patients developed new cases of myopathy during the average follow-up of 3.9 months. The cumulative incidence rate for the overall population was 0.32 per 100 person-months based on the above formula.

The incidence density was then calculated for the statin user and the statin interacter groups. Table 3.17 provides information on incidences of myopathy for both groups.

Table 3.17: Number of patients, sum of follow-up months, number of myopathy cases, and incidence of myopathy per 100 person-months by statin users and statin interacters

	Statin Users	Statin Interacters
Number of patients	5,817	3,005
Sum of follow-up months (person-months)	23,369	11,656
Number of myopathy cases (%)	49 (0.8)	64 (2.1)
Incidence[a]	0.21	0.54

[a.] New myopathy cases per 100 person-months

As seen from Table 3.17, statin interacters had higher incidence density of myopathy (0.54 per 100 person-months) than statin users (0.21 per 100 person-months). When the two groups were compared using chi-square analysis, there was a statistically significant ($\chi 2 = 25.97$; df = 1; $p < 0.001$) difference in the number of myopathy cases between two groups. The odds of myopathy within the two groups controlling for a variety of risk factors will be discussed in objective eight.

Objective 6: To describe demographic characteristics of the study population based on presence or absence of myopathy.

Tale 3.18 provides information on age, sex, and ethnicity/race based on whether the patient has experienced myopathy for each of the two cohorts.

Table 3.18: Age, gender, and ethnicity/race by presence or absence of myopathy for statin users and statin interacter groups

Demographic Characteristics	Statin Users N = 5,817		Statin Interacters N = 3,005	
	Myopathy N = 49	No Myopathy N = 5,768	Myopathy N = 64	No Myopathy N = 2,941
Age (Years) Mean (SD)	50.3 (9.6)	51.1 (10.0)	54.0 (9.3)	51.3 (9.7)
Gender				
Female (%)	33 (67.3)	3,199 (55.5)	43 (67.2)	1,918 (65.2)
Males (%)	16 (32.7)	2,569 (44.5)	21 (32.8)	1,023 (34.8)
Ethnicity/Race				
Whites (%)	24 (48.9)	2,124 (36.8)	28 (43.8)	1,210 (41.1)
Blacks (%)	9 (18.4)	1,257 (21.8)	12 (18.8)	669 (22.8)
Hispanics (%)	14 (28.6)	1,934 (33.5)	19 (29.7)	799 (27.2)
Asians (%)	N/A	125 (2.2)	1 (1.5)	70 (2.4)
Others (%)[a]	2 (4.1)	328 (5.7)	4 (6.2)	193 (6.5)

[a.] Others includes all other ethnicities besides those mentioned above

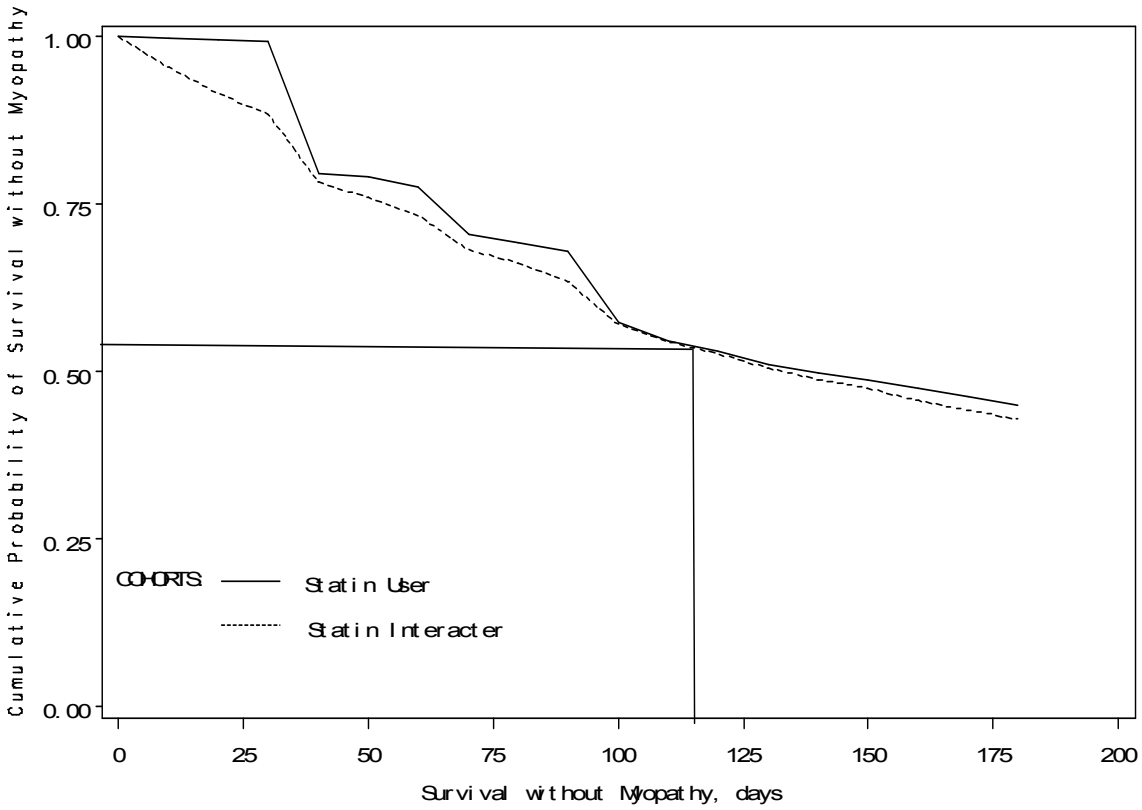
The proportion of females was greater for patients experiencing myopathy than those with no myopathy for both groups (Table 3.18). The percent of Blacks, Asians and other ethnic groups was lower for patients with myopathy compared to those without myopathy; but the percent of Whites was higher for those patients experiencing myopathy than those without myopathy for both groups. In the statin user group, the proportion of Hispanics was smaller for patients with myopathy (28.6%) than those without myopathy (33.5%). Also, the patients with myopathy were slightly younger than patients without myopathy. However, in the statin interacter group, not only was the

percent of Hispanics greater for patients having myopathy (29.7%) compared to those without myopathy (27.2%), also patients with myopathy were older than those without myopathy. The association of these demographic variables with risk of myopathy will be discussed in objective 9.

Objective 7: To describe the "time to occurrence of myopathy" in patients receiving statins and potentially interacting medications, and patients receiving statins without potentially interacting medications.

This objective was addressed using Kaplan-Meier survival analysis. Kaplan-Meier survival analysis describes the time to survival without myopathy in context of incomplete (censored) information. Figure 3.2 shows the survival curves for the statin user and statin interacter groups.

Figure 3.2: Kaplan-Meier curves for statin user and statin interacter groups



As seen from the Figure 3.2, the probability of 180 days survival (without myopathy) was higher for statin user group (0.45) compared to statin interacters (0.42). There was a statistically significant difference ($\chi 2 = 10.77$; df = 1; $p < 0.05$) in survival times between two groups. As seen from the graph, for a short time period, approximately between 100 and 120 days, the probability of survival is higher in the statin interacter group than the statin user group. Table 3.19 provides information on the probability of survival without myopathy and the mean survival times for the statin user and statin interacter groups.

Table 3.19: Probability of survival without myopathy and mean survival time for statin users and statin interacters

	Statin User	Statin Interacter
Probability of 1-month survival	0.99	0.88
Probability of 3-months survival	0.68	0.63
Probability of 6-months survival	0.45	0.42
Mean (SE)[a] Survival, days[b]	120 (0.81)	115 (1.19)

[a.] S.E. – Standard Error. Standard Error was reported in the output instead of standard deviation
[b.] The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

Objective 8: To assess the relationship between the development of myopathy and use of potentially interacting medications with statins, while controlling for other risk factors for myopathy

The relationship between presence or absence of myopathy and use of potentially interacting medications with statins was assessed using logistic regression. The dependent variable was a dichotomous variable where 1 = presence of myopathy and 0 = absence of myopathy. The risk factors that were controlled for included age, gender, ethnicity/race, presence of diabetes, number of comorbidities, type of statin used, dose of statin and duration of statin treatment. As mentioned earlier in the testing of logistic regression assumptions section, the Asian ethnicity/race category was collapsed with the other ethnicities/races category because the expected cell count was less than one. Also, lovastatin and fluvastatin users were collapsed into one single category of other statins as

25% of cells had an expected count of less than five. The physician specialty variable was not included in the analysis due to missing data.

The logistic model for the odds of developing myopathy (i.e., Y = 1) for an any given subject i is

$$Yi = \frac{\exp(g(xi))}{1 + \exp(g(xi))}$$

Where g(xi) is the usual linear equation:

$$g(xi) = \beta_0 + \beta_1 X_1 + \ldots\ldots + \beta_k X_k$$

With constant β_0, coefficients β_j, and predictors X_j for k predictors (j = 1, 2, 3 … k).

The logistic regression model showed an improvement in fit based on the global chi-square test ($\chi^2 = 61.2$; df = 13; $p < 0.0001$) and an acceptable functional form based on the Hosmer and Lemeshow statistic ($\chi^2 = 15.1$; df = 8; $p > 0.05$). Table 3.20 provides information on the results of the regression analysis for odds of developing myopathy.

Table 3.20: Logistic regression analysis results to assess the relationship between odds of developing myopathy and use of potentially interacting medications

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value	Odds Ratio	95% Confidence Interval for Odds Ratio	
							Lower	Upper
Receipt of PIM[a]	1.000	0.200	24.87	1	< 0.0001*	2.720	1.83	4.03
Age	0.008	0.011	0.65	1	0.419	1.009	0.988	1.030
Gender (Female)[b]	0.275	0.205	1.79	1	0.179	1.317	0.881	1.970
Ethnicity (Black)[c]	-0.385	0.264	2.12	1	0.145	0.681	0.406	1.142
Ethnicity (Hispanic)[c]	-0.214	0.230	0.867	1	0.352	0.807	0.514	1.268
Ethnicity (Other)[c]	-0.507	0.409	1.537	1	0.215	0.602	0.270	1.342
Diabetes[d]	0.140	0.197	0.511	1	0.475	1.151	0.783	1.692
Comorbidities	0.320	0.088	13.202	1	0.0003*	1.377	1.159	1.637
Atorvastatin[e]	0.271	0.302	0.800	1	0.3710	1.311	0.725	2.372
Simvastatin[e]	0.068	0.341	0.040	1	0.8410	1.071	0.549	2.091
Other statins[e]	-1.085	0.759	2.04	1	0.153	0.388	0.076	1.497
Duration of statin use	-0.002	0.000	9.62	1	0.001*	0.997	0.995	0.999
Dose of statin[f]	-0.159	0.228	0.489	1	0.484	0.853	0.545	1.333

* $p<0.05$
[a.] PIM – Potentially interacting medication
[b.] Reference category is male
[c.] Reference category is Whites
[d.] Reference category is absence of diabetes
[e.] Reference category is pravastatin
[f.] Reference category is low doses of statin

As seen from Table 3.20, the odds of myopathy increases when a patient is using statins and potentially interacting medications compared to those who use statins without potentially interacting medications. The 95% CI showed that the odds had a range of 1.83 to 4.03 times greater if the patient used a potentially interacting medication. In

addition, comorbidities and duration of statin use were statistically significant, which is discussed under objective 9.

Hypothesis 8: The odds of developing myopathy will be higher for statin interacters as compared to statin users, controlling for other factors.

Based on results of logistic regression (Table 3.20), the odds of developing myopathy was significantly higher (OR: 2.72; 95% CI: 1.83–4.03) for statin interacters than statin users. Statin interacters had two times higher odds of developing myopathy than statin users, while controlling for other factors. Based on these results, hypothesis 8 was not rejected.

Objective 9: To determine the risk factors (demographic factors, health risk factors, treatment factors and physician-related factors) for myopathy.

Logistic regression analysis was conducted to determine the risk factors associated with developing myopathy. Two logistic regression models were analyzed. In the first model, the analysis included all patients and all factors except those involving PIM characteristics as statin users never received PIMs and therefore, that information was not available for them. In order to evaluate PIM characteristics as risk factors for myopathy, a separate logistic analysis was done only on statin interacters. The variable physician specialty was not included in the analysis due to missing data, as mentioned before. Therefore, hypothesis 23 could not be evaluated. The results of logistic

regression analysis that included all the patients are discussed first followed by the results of the analysis of statin interacters.

Table 3.20 provides information on the results of logistic regression analysis. As seen from the Table 3.20, the odds of developing myopathy were significantly associated with the number of comorbidities and duration of statin use. The odds of developing myopathy increased with an increasing number of comorbidities (OR: 1.377; 95% CI: 1.159–1.637). Even though decreasing duration of statin use was significantly associated with odds of developing myopathy, the difference was only minimal (OR: 0.997; 95% CI: 0.995-0.999). Based on the results of this analysis, hypotheses 9 to 19 are discussed.

Hypothesis 9: The odds of developing myopathy will increase with increasing age, while controlling for other factors.

Based on the results of logistic regression analysis (Table 3.20), increasing age had higher odds of developing myopathy (OR: 1.009; 95% CI: 0.988 –1.030); however, these results were not statistically significant. Therefore, hypothesis 9 was rejected.

Hypothesis 10: The odds of developing myopathy will be higher for females than males, while controlling for other factors.

Based on the results shown in Table 3.20, hypothesis 10 was rejected. There was no statistically significant difference in odds of developing myopathy between females and males (OR: 1.317; 95% CI: 0.881-1.970).

Hypothesis 11: There will be no difference in the odds of developing myopathy based on ethnicity/race, while controlling for other factors.

Logistic regression analysis revealed that there was no statistically significant difference in odds of developing myopathy based on ethnicity/race (Blacks - OR: 0.681; 95% CI: 0.406-1.142, Hispanics - OR: 0.807; 95% CI: 0.514-1.268, Other - OR: 0.602; 95% CI: 0.270-1.342). Therefore, hypothesis 11 was not rejected.

Hypothesis 12: The odds of developing myopathy will be higher for patients with diabetes than those without diabetes, while controlling for all other factors.

There was no statistically significant difference in the odds of developing myopathy (OR: 1.151; 95% CI: 0.783 – 1.692) between patients with diabetes and those without diabetes. Based on these results, hypothesis 12 was rejected.

Hypothesis 13: The odds of developing myopathy will increase with increasing number of comorbidities, while controlling for other factors

Based on the results shown in Table 3.20, there was statistically significant increase in the odds of developing myopathy with an increasing number of comorbidities. Specifically, the odds of developing myopathy increased 1.37 times with an increasing number of comorbidities (OR: 1.377; 95% CI: 1.159 - 1.637). Therefore, hypothesis 13 was not rejected.

Hypothesis 14: The odds of developing myopathy will be higher for patients using simvastatin as compared to pravastatin, while controlling for other factors.

Based on the results of logistic regression analysis (Table 3.20), there was no statistically significant difference in the odds of developing myopathy for patients on simvastatin compared to those on pravastatin (OR: 1.071; 95% CI: 0.549–2.091). Thus, hypothesis 14 was rejected.

Hypothesis 15: The odds of developing myopathy will be higher for patients using atorvastatin as compared to pravastatin, while controlling for other factors.

The results of the regression analysis (Table 3.20) revealed there was no difference in the odds of developing myopathy for patients using atorvastatin as compared to those using pravastatin (OR: 1.311; 95% CI: 0.725–2.372). Based on these results, hypothesis 15 was rejected.

Hypothesis 16: The odds of developing myopathy will be higher for patients using fluvastatin/lovastatin as compared to pravastatin, while controlling for other factors

Fluvastatin and lovastatin users were combined to form one group. This was done to increase the cell count due to the small number of fluvastatin and lovastatin users. Based on the results of the logistic regression (Table 3.20), after combining both users, there was no statistically significant difference in the odds of developing myopathy for patients using fluvastatin and lovastatin compared to patients using pravastatin (OR:

0.388; 95% CI: 0.076–1.497). Therefore, both hypothesis 16 and hypothesis 17 were rejected.

Hypothesis 17: The odds of developing myopathy will be higher for patients on higher doses of statins than lower doses of statins, controlling for other factors.

The doses of statins were categorized into two groups based on the comparative efficacy of the statins on lipid levels (Table 2.7 in Chapter 2). All the doses in group I are lower and have lower reduction in lipid levels as compared to doses of statins in group II. Based on the logistic regression analysis results shown in Table 3.20, there was no statistically significant difference in the odds of developing myopathy between patients on higher doses of statins and those on lower doses of statins (OR: 0.853; 95% CI: 0.545-1.333). Therefore, hypothesis 18 was rejected.

Hypothesis 18: The odds of developing myopathy will increase with increasing duration of use of statin, while controlling for other factors.

Based on the results shown in Table 3.20, hypothesis 19 was rejected. The odds of developing myopathy decreased with increasing duration of statin use (OR: 0.997; 95% CI: 0.995–0.999). Even though the results were statistically significant, the difference was minimal. Nevertheless, hypothesis 19 was rejected.

In order to evaluate the association between PIM characteristics and risk of myopathy, logistic regression analysis was conducted only on statin interacters. Table

3.21 provides information on logistic regression analysis conducted on statin interacters to determine PIM characteristics that are risk factors for myopathy.

Table 3.21: Logistic regression analysis results to determine PIM characteristics that risk factors for myopathy for statin interacters

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value	Odds Ratio	95% Confidence Interval for Odds Ratio	
							Lower	Upper
Age	0.034	0.016	34.15	1	<0.001*	1.035	1.004	1.067
Gender (Female)[a]	0.029	0.277	0.011	1	0.916	1.030	0.598	1.773
Ethnicity (Black)[b]	-0.233	0.355	0.432	1	0.511	0.792	0.394	1.589
Ethnicity (Hispanic)[b]	0.027	0.312	0.008	1	0.930	1.028	0.558	1.893
Ethnicity (Other)[b]	-0.299	0.497	0.363	1	0.547	0.741	0.280	1.963
Diabetes[c]	0.056	0.264	0.045	1	0.832	1.058	0.631	1.774
Comorbidities	0.299	0.113	7.047	1	0.008*	1.349	1.081	1.682
Atorvastatin[d]	0.275	0.403	0.465	1	0.495	1.316	0.597	2.902
Simvastatin[d]	0.384	0.440	0.759	1	0.383	1.468	0.619	3.481
Other statins[d]	-1.101	1.067	1.063	1	0.302	0.332	0.041	2.696
Duration of statin use	-0.001	0.000	3.959	1	0.047*	0.998	0.997	1.000
Dose of statin[e]	-0.409	0.324	1.599	1	0.206	0.664	0.352	1.252
Significance of drug interaction								
Level 2[f, g]	-0.278	0.305	0.834	1	0.361	0.757	0.416	1.376
Level 3[f, h]	-1.271	1.038	1.500	1	0.221	0.280	0.037	2.145
Time of receipt of PIM[i, j]	0.240	0.345	0.485	1	0.486	1.272	0.647	2.500
Duration of PIM[j] use	-0.002	0.002	1.029	1	0.310	0.997	0.992	1.002

* $p<0.05$
[a.] Reference category is male
[b.] Reference category is Whites
[c.] Reference category is absence of diabetes
[d.] Reference category is pravastatin
[e.] Reference category is low doses of statin
[f.] Reference category is Level 1 which is defined as severe or potentially life-threatening.
[g.] Level 2 is defined as an interaction that causes detoriation in patients' clinical status.
[h.] Level 3 is defined as moderate to minor side effects.
[i.] Reference category is PIM received after start of statin therapy
[j.] PIM – Potentially interacting medication

A sub-group analysis on statin interacters as shown in Table 3.21 revealed the same risk factors as shown in Table 3.20 to be significantly associated with odds of developing myopathy. In addition, increasing age was associated with higher odds of developing myopathy (OR: 1.035; 95% CI: 1.004-1.067). Based on the results of this sub-group analysis, hypotheses 20 to 22 are discussed.

Hypothesis 19: The odds of developing myopathy will increase with increasing level of significance of drug interaction, while controlling for other factors.

Based on the results of logistic regression shown in Table 3.21, there was no statistically significant difference in the odds of developing myopathy based on level of significance of drug interaction. Therefore, hypothesis 19 was rejected.

Hypothesis 20: There will be no difference in the odds of developing myopathy based on whether the potentially interacting medication was given before or after the start of statin therapy, while controlling for other factors.

The results of regression analysis revealed that there was no difference in the odds of developing myopathy based on whether the potentially interacting medication was given before or after the start of statin therapy (OR: 1.272; 95% CI: 0.647–2.500). Therefore, hypothesis 20 was not rejected.

Hypothesis 21: The odds of developing myopathy will increase with increased duration of potentially interacting medication use, while controlling for other factors.

Logistic regression analysis (Table 3.21) revealed that there was no statistically significant difference in the odds of developing myopathy with increased duration of PIM use (OR: 0.997; 95% CI: 0.992-1.002). Therefore, hypothesis 21 was rejected.

SUMMARY OF THE STUDY HYPOTHESES TESTS

Table 3.22 provides a summary of the results of study hypotheses tests.

Table 3.22: Results of the hypotheses tests

Study Hypothesis	Description	Rejected/Not Rejected
Evaluation of factors that are associated with the receipt of potentially interacting medication		
Hypothesis 1	There will be no difference in the odds of receipt of potentially interacting medication based on type of statin, while controlling for other factors.	Rejected
Hypothesis 2	There will be no difference in the odds of receipt of potentially interacting medication based on dose of statin, while controlling for other factors. .	Not Rejected
Hypothesis 3	The odds of receipt of potentially interacting medication will increase with increasing age, while controlling for other factors.	Rejected
Hypothesis 4	There will be no difference in the odds of receipt of potentially interacting medication based on gender, while controlling for other factors	Rejected

Table 3.22: Results of the hypotheses tests (continued)

Study Hypothesis	Description	Rejected/ Not Rejected
Hypothesis 5	There will be no difference in the odds of receipt of potentially interacting medication based on ethnicity/race, while controlling for other factors.	Rejected
Hypothesis 6	The odds of receipt of potentially interacting medication will increase with increasing number of comorbidities, while controlling for other factors.	Not rejected
Hypothesis 7	There will be no difference in the odds of receipt of potentially interacting medication based on physician specialty, while controlling for other factors.	Did not test
Evaluation of risk factors that are associated with the development of myopathy		
Hypothesis 8	The odds of developing myopathy will be higher for statin interacters than for statin users, while controlling for other factors.	Not rejected
Hypothesis 9	The odds of developing of myopathy will increase with increasing age, while controlling for other factors.	Rejected
Hypothesis 10	The odds of developing myopathy will be higher for females than males, while controlling for other factors.	Rejected
Hypothesis 11	There will be no difference in the odds of developing myopathy based on ethnicity/race, while controlling for other factors.	Not Rejected
Hypothesis 12	The odds of developing myopathy will be higher for patients with diabetes than those without diabetes, while controlling for other factors.	Rejected
Hypothesis 13	The odds of developing myopathy will increase with increasing number of comorbidities, while controlling for other factors.	Not Rejected
Hypothesis 14	The odds of developing myopathy will be higher for patients using simvastatin as compared to pravastatin, while controlling for other factors.	Rejected

Table 3.22: Results of hypotheses tests (continued)

Study Hypotheses	Description	Rejected/Not Rejected
Hypothesis 15	The odds of developing myopathy will be higher for patients using atorvastatin as compared to pravastatin, while controlling for other factors.	Rejected
Hypothesis 16	The odds of developing myopathy will be higher for patients using fluvastatin/lovastatin as compared to pravastatin, while controlling for other factors.	Rejected
Hypothesis 17	The odds of developing myopathy will be higher for patients on higher doses of statins than lower doses of statins, while controlling for other factors.	Rejected
Hypothesis 18	The odds of developing myopathy will increase with increasing duration of statin use, while controlling for other factors.	Rejected
Hypothesis 19	The odds of developing myopathy will increase with increasing level of significance of drug interaction, while controlling for other factors.	Rejected
Hypothesis 20	There will be no difference in the odds of developing myopathy based on whether the potentially interacting medication was given before/ after the start of statin therapy, while controlling for other factors.	Not Rejected
Hypothesis 21	The odds of developing myopathy will increase with increasing duration of PIM use, while controlling for other factors.	Rejected
Hypothesis 22	There will be no difference in odds of developing myopathy based on physician specialty, while controlling for other factors.	Did not test

SENSITIVITY ANALYSIS

A sensitivity analysis was conducted on the duration of statin use variable. Duration of statin use was originally defined as the time period a patient was exposed to statin before the end of observation period. The end of the observation period is defined when any one of the following three events occur: 1) diagnosis of myopathy; 2) discontinues statin therapy or PIM use; 3) end of 180 days follow-up period. Discontinuation of statin therapy was defined as a gap of greater than 45 days between two refills. In the sensitivity analysis, the criterion for discontinuation of statin therapy was defined as a gap of greater than 60 days between two refills.

Based on this criterion, a total of 8,911 patients were included in the study of which 5,817 patients were statin users and 3,094 were statin interacters. Objectives four, five, seven, eight and nine were re-analyzed with this new end-point. Results are presented in Appendix D. The results of all objectives when a gap greater than 60 days was allowed between refills were similar to the original results when a gap of greater than 45 days was allowed.

CHAPTER 4

DISCUSSION AND CONCLUSIONS

The present study examined the risk of myopathy associated with the use of statins and potentially interacting medications in Texas Medicaid population. This chapter discusses the results of the study by comparing and contrasting them with previous research, and finally presenting the conclusion. First, the background for the study is reviewed, followed by the present study overview, discussion of the objectives, study limitations, and finally study implications and conclusions.

STUDY BACKGROUND

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statins as they are commonly called are the most widely used drugs for the management of hyperlipidemia. The management of hyperlipidemia is essential in the prevention of CHD. Primary, secondary, and angiographic trials have demonstrated the beneficial effects of statins in treatment of hyperlipidemia and in reduction of CHD-related morbidity and mortality (as discussed in Section I).

Statins as a class of drugs are generally well tolerated; however, adverse events have been associated with statins both as monotherapy and in combination therapy with other agents. Concern over the safety of statins was heightened by the worldwide

withdrawal of cerivastatin in 2001, a drug that was thought to be relatively free of adverse effects over the four years it was marketed.[376,377] The major side-effect associated with cerivastatin as well as other statins is myopathy.

Myopathy is a general term referring to disorders of muscles ranging from mild myalgia to severe rhabdomyolysis. The risk of statin-associated myopathy further increases in the presence of a number of risk factors.[378] One of the most important risk factors is concurrent use of PIMs with statins. Statins in combination with PIMs which inhibit their metabolism, increase the blood levels of statins, thereby increasing the risk of myopathy. One study estimated the risk of myopathy to be 12-fold higher in patients using a statin-fibrate combination versus those using statins by themselves.[379] There is very limited information on the risk of myopathy when statins are taken with other potentially interacting medications and the risk factors that increase the probability of myopathy. The next section discusses the studies that have estimated the risk of myopathy.

Observational studies evaluating the risk of myopathy

Four known observational studies estimated the incidences of myopathy. Two of these studies were conducted using the GPRD database and focused on rhabdomyolysis,

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[376] Psaty BM, Furberg CD, Ray WA, et al. Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis. *JAMA* 2004;292:2622-2631.
[377] Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002;346:539-540.
[378] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[379] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.

and the other two studies were conducted on the US population using data from managed care and included hospitalized cases of myopathy.

The earliest study conducted using the UK population estimated the incidence of myopathy as 2.3 per 10,000 person-years for patients using lipid lowering drugs.[380] The relative risk was of myopathy was 7.6 (95% CI: 1.4–41.3) for statin users and 42.4 (95% CI: 11.6–170.5) for fibrate users compared with non-users. Another study that used the same database identified only one case of rhabdomyolysis among 52,000 patients receiving lipid lowering agents.[381] This patient was on statin-fibrate combination therapy.

Graham and colleagues[382] used claims data from 11 managed care organizations to establish the incidence of hospitalized rhabdomyolysis across US. The incidence of myopathy was 0.44 per 10,000 person-years for statin users (excluding cerivastatin) and 5.98 per 10,000 person-years for statin-fibrate combination users. The relative risk of myopathy increased for patients aged 65 years and older, and for patients with diabetes mellitus. As compared to statin users, fibrate users had a 5.5-fold greater risk of myopathy and statin-fibrate combination users had a 12.2-fold increase in risk of myopathy.[383]

A more recent study used administrative claims database from diverse regions in the US to evaluate the incidences of hospitalizations related to adverse effects including

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[380] Gaist D, Garcia Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565-9.
[381] Black C, Jick H. Etiology and frequency of rhabdomyolysis. *Pharmacotherapy* 2002;22:1524-26.
[382] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[383] Ibid.

myopathy for lipid lowering agents. Incidence of hospitalizations for myopathy in patients treated only with statins varied from 1.58 for fluvastatin to 3.84 for pravastatin per 10,000 person-years. Risk of hospitalizations due to myopathy increased in the presence of hypertension (RR: 5.13; 95% CI: 2.42–10.85) and if patients received potentially interacting medications concurrently with statins (RR: 6.01; 95% CI: 2.08–17.38).[384]

Only one known study has evaluated the risk of myopathy in patients using PIMs concurrently with statins.[385] However, not all drugs listed by the ACC/AHA/NHLBI clinical advisory on safety of statins were included in the analysis. The study findings were also limited by lack of control for other important risk factors that increase the probability of myopathy and included only hospitalized cases of myopathy. Most other studies evaluated only the association between risk of myopathy and use of statins with a secondary focus on statin-fibrate combination use and risk of myopathy.[386,387] Given the sparse information about risk and risk factors of myopathy in patients using statins and PIMs, this study aimed to fill this gap in literature.

PRESENT STUDY OVERVIEW

The purpose of this study was to estimate the incidence and risk factors of myopathy in patients using a statin product with and without PIMs using Texas Medicaid

[384] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[385] Ibid.
[386] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[387] Gaist D, Garcia Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565-9.

database. The study objectives were addressed in patients who were new users of statins, using five years of data. The study included patients with a greater number of risk factors and a greater number of PIMs than previous studies. The large sample size (N=8,222) provided sufficient statistical power to detect differences between the two cohorts. Incidences for statin users and statin interacters were calculated and logistic regression analyses were used to determine the risk of myopathy and risk factors associated with myopathy. Next, study objectives will be discussed by comparing and contrasting the study results with findings of previous studies.

STUDY OBJECTIVES:

Two goals corresponding to nine objectives and 23 hypotheses were addressed in this study (Table 4.1). The results of these objectives are discussed in light of current literature.

Table 4.1: Study objectives and hypotheses

Study Objectives	Hypotheses
Evaluation of trends in prescribing patterns of potentially interacting medications with statins	
1. To provide descriptive statistics on type and dose of statins.	N/A
2. To provide descriptive statistics on type of potentially interacting medications.	N/A
3. To describe demographic characteristics of study population based on whether or not they receive potentially interacting medications**.**	N/A
4. To identify demographic, health-related, treatment, and physician-related factors that are associated with the receipt of PIMs.	1-7
Evaluation of incidence and risk factors for myopathy in patients receiving statins with and without potentially interacting medications	
5. To estimate the overall incidence of myopathy among study population.	N/A
6. To describe demographic characteristics of study population based on presence or absence of myopathy.	N/A
7. To describe the "time to occurrence of myopathy" in patients receiving statins and potentially interacting medications, and patients receiving statins without potentially interacting medications.	N/A
8. To assess the relationship between the development of myopathy and use of potentially interacting medications with statins, while controlling for other risk factors for myopathy.	8
9. To determine the risk factors (demographic factors, health risk factors, treatment factors and physician-related factors) for myopathy.	9-22

STATIN CHARACTERISTICS

The first objective of the study was to describe the type and dose of statin therapy used by Texas Medicaid population. The most commonly prescribed statins were atorvastatin (55.5%), simvastatin (25.2%), pravastatin (13.1%), fluvastatin (5.3%), and lovastatin (0.9%). These results were similar to results of another study that assessed the drug utilization patterns in Texas Medicaid.[388] Both studies had a similar hierarchy of use of statin drugs. These results were also consistent with national trends in statin use. In a recent study that used data from the National Ambulatory Medical Care Survey and National Hospital Medical Care survey, in 2002, the most frequently used statin was atorvastatin (approximately 50%), followed by simvastatin, pravastatin, fluvastatin and lovastatin.[389] This national study included patients above the age of 65 years; nevertheless, the trends in statin use were similar to the current study.

In the present study, a majority of the patients (80.1%) were initiated on recommended doses of statins. Based on package inserts, the recommended starting doses were as follows: atorvastatin 10 or 20 mg once daily;[390] simvastatin 20 or 40 mg once daily;[391] pravastatin 40 mg once daily;[392] fluvastatin 40 mg once daily;[393] and lovastatin 20 mg once daily.[394] These results were also consistent with a previous study

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[388] Dastani HB. Assessment of drug utilization patterns, medication compliance, and physician adherence to lipid and safety monitoring guidelines among patients on lipid-lowering drugs in the Texas Medicaid system. Austin, TX: The University of Texas at Austin; 2005. Dissertation.

[389] Ma J, Shegal NL, Ayanian JZ. National trends in statin use by coronary heart disease risk category. *PLoS Med* 2005;2:e123.

[390] Lipitor (atorvastatin) [package insert]. Morris Plains, NJ: Pfizer; 2005.

[391] Zocor. (simvastatin) [packcage insert]. Whitehouse Station, NJ: Merck & Co. Inc.; 2005.

[392] Pravachol (pravastatin) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2004.

[393] Lescol (fluvastatin) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2003.

[394] Mevacor (lovastatin) [package insert]. Whitehouse Station, NJ: Merck & Co. Inc.; 2005.

that assessed statin utilization patterns in Texas Medicaid where most patients (78.7%) were initiated on recommended starting doses.[395]

When type and dose of statins were broken down by the two cohorts, the statin user and statin interacter groups, both groups were similar. However, there was a greater use of pravastatin in the statin interacter group (14.2%) than the statin user group (12.6%). Among all patients who received statins and PIMs concurrently, patients using pravastatin received the highest percent of PIMs (36.0%) compared to patients using other statins. This is not surprising given the fact that pravastatin is the only statin which is not metabolized by the CYP450 system; thus, there is less likelihood of drug interaction.[396] Therefore, greater numbers of patients were using pravastatin and PIMs together. These results were also consistent with another study where among all statin users who received potentially interacting medications, patients on pravastatin received the highest percentage of potentially interacting medications.[397] However, Etemad et al. found patients on pravastatin had the lowest frequency of receiving potentially interacting medications as compared to other statin users.[398] One explanation could be that the time period selected for that study was right around withdrawal of cerivastatin (01/01/00 – 12/31/01). Therefore, physicians may have been less aware and more liberal in prescribing PIMs with other statins. The current study as well as the study by Cziarky

[395] Dastani HB. Assessment of drug utilization patterns, medication compliance, and physician adherence to lipid and safety monitoring guidelines among patients on lipid-lowering drugs in the Texas Medicaid system. Austin, TX: The University of Texas at Austin; 2005. Dissertation.
[396] Bottorf M. Safety and statins: Pharmacologic and clinical perspective. *Am J Manag Care* 2004;4:S30-S37.
[397] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[398] Etemad LR, Fairchild C, Waldeck R. *Prevalence and cost implications of potential interactions with statin medications in a managed care population.* ISPOR Ninth Annual International Meeting 2004. Washington, D.C.

and colleagues[399] included time periods two to three years after withdrawal of cerivastatin. Therefore, physicians may have been more aware that there is relatively less risk of prescribing PIMs with pravastatin compared to other statins, given the withdrawal of cerivastatin.

CHARACTERISTICS OF POTENTIALLY INTERACTING MEDICATIONS

The second objective was to provide descriptive statistics on the type of potentially interacting medications received in this study. The ACC/AHA/NHLBI clinical advisory on use and safety of statins has provided a list of PIMs which potentially increase the risk of statin-associated myopathy.[400] These medications are fibrates, niacin, cyclosporine, azole antifungals, macrolide antibiotics, HIV protease inhibitors, nefazodone, calcium channel blockers, and amiodarone. All of these medications were included in the current study except cyclosporine and HIV protease inhibitors.

The most frequently used PIMs with statins were macrolide antibiotics (40.8%), calcium channel blockers (29.2%), and fibrates (12.6%) comprising 82.6% of all PIM prescriptions. These results were consistent with another study conducted in the Veterans Affairs Health Care System where fibrates and calcium channel blockers were the top two PIMs prescribed with simvastatin.[401] This study did not include short-term

[399] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[400] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[401] Petropoulos JB, Bello-Quintero CE. Frequency of simvastatin prescriptions with potentially interacting medications in a Veterans Affairs health care system. *J Manag Care Pharm* 2004;10:239-43.

medications such as antibiotics. However, in a Canadian study macrolide antibiotics were the most frequently used PIMs with statins.[402]

When type of PIM used was classified based on level of significance of drug interaction,[403] more than half the patients (56.4%) received PIMs with a Level 1 significance of drug interaction, which is defined as a potentially severe or life threatening interaction. This is because fibrates and antibiotics were included in Level 1 and more than half the patients received these drugs. The increased prescribing of these drugs with statins may be because health care professionals may judge that the benefits outweigh the risks and thus prescribe the drugs together.

DEMOGRAPHIC CHARACTERISTICS

Objectives three and six were related to demographic characteristics of the patient population. Objective three aimed to describe the patient population based on whether the patient utilized statin therapy with or without PIM. Objective six described demographics based on the presence or absence of myopathy. First, the overall demographics of patients in Texas Medicaid are discussed.

A majority of patients in this study were females (58.9%). These results were consistent with the current statistics of Texas Medicaid which is comprised mainly of

[402] Einarson TR, Metge CJ, Iskedjian M, et al. An examination of the effect of cytochrome P450 drug interactions of hydroxymethylglutaryl-coenzyme A reductase inhibitors on health care utilization: a Canadian population-based study. *Clin Ther* 2002;24:2126-36.
[403] Drug Interaction Facts. Wolters Kluwer Health, Inc, 2003-2005. Available at: http://www.efactsonline.com/Fac/servlet/MainPage. Accessed on: January 2005

women (56%) and non-disabled children (59%).[404] This study included patients between the ages of 21-64 years of age. Patients aged 65 years and older were not included in the study as their medical claims may be incomplete due to dual eligibility in Medicare and Medicaid. The mean age of the patient population was 51.2 years. This result was similar with a previous study conducted on statin users enrolled in Texas Medicaid; the average age of statin users in that study was 49.7 years.[405] However, in other studies conducted in primary care settings the mean age of patients was 58.5 years.[406,407] This difference may be due to exclusion of patients aged 65 and above in the current study.

Whites comprised 38.4% of the total patient population followed by Hispanics (31.3%), and Blacks (22.1%). A greater percentage of Whites were receiving statins than other ethnic groups. These results were not surprising given the statistics from the state of Texas which reveal a higher prevalence of hyperlipidemia in Whites than in other ethnic groups.[408] These results were also consistent with a previous study conducted on statin users in Texas Medicaid where 42.7% were Whites, 32.7% patients were Hispanics, and 22.5% patients were Blacks.[409] A national sample of patients showed

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[404] Texas Health and Human Services. Clients and Benefits. *Texas Medicaid in Perspective* 2004;4-1 - 4-28.

[405] Dastani HB. Assessment of drug utilization patterns, medication compliance, and physician adherence to lipid and safety monitoring guidelines among patients on lipid-lowering drugs in the Texas Medicaid system. Austin, TX: The University of Texas at Austin; 2005. Dissertation.

[406] White J, Chang E, Leslie S. Patient adherence with HMG reductase inhibitor therapy mong users of two types of prescription services. *JMCP* 2002;8:186-191.

[407] Harley CR, Setareh WA, McDonough KL. Cholesterol management in a population of managed care enrollees. *J Clin Outcomes Manage* 2003;10:147-154.

[408] Cardiovascular Disease (CVD) in Texas: A surveillance report and program strategy. Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health, 2003. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvdsurv2003.pdf. Accessed on: May 04, 2006

[409] Dastani HB. Assessment of drug utilization patterns, medication compliance, and physician adherence to lipid and safety monitoring guidelines among patients on lipid-lowering drugs in the Texas Medicaid system. Austin, TX: The University of Texas at Austin; 2005. Dissertation.

similar trends; based on ATP II guidelines, a greater percentage of Whites (29.5%) qualified for dietary and drug therapy than Hispanics (24.7%), and Blacks (18.2%).[410]

Objective 3: To describe demographic characteristics of the study population based on whether or not they receive potentially interacting medications.

Both cohorts had a greater number of females than males. This was not surprising considering that a greater percent of females are enrolled in Texas Medicaid than males.[411] However, the statin interacter group had a higher percent of females (65.3%) than the statin user group (55.6%). This means that more females received statins and PIMs concurrently. This may be because some of the PIMs prescribed such as macrolide antibiotics and azole antifungals, which comprised approximately 51% of all PIMs prescribed, were prescribed primarily for conditions experienced by females such as vaginal infections. These results are similar to a Canadian study which found more females (55.5%) received PIMs with statins than males (44.5%).[412]

The average age was similar for both the statin interacter (51.4 years) and statin user groups (51.1 years). This may be surprising as increasing age is associated with increased comorbidities and thus, increased use of PIMs. However, this study did not include patients above the age of 65 years and therefore, the average age may be similar between two groups. Table 3.5 depicts each cohort broken by age group and gender.

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[410] Hoerger TJ, Bala MV, Bray JW, et al. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *Am J Cardiol* 1998;82:61-5.

[411] Texas Health and Human Services. Clients and Benefits. *Texas Medicaid in Perspective* 2004;4-1 - 4-28.

[412] Einarson TR, Metge CJ, Iskedjian M, et al. An examination of the effect of cytochrome P450 drug interactions of hydroxymethylglutaryl-coenzyme A reductase inhibitors on health care utilization: a Canadian population-based study. *Clin Ther* 2002;24:2126-36.

The statin user group had more males under the age of 50 and more females above the age of 50. A chi-square analysis revealed that this difference was statistically significant ($\chi 2 = 88.29$; d.f. = 4; $p < 0.0001$). This means that males under the age of 50 are more likely to receive statins than females. Previous research has shown that more males receive lipid tests than females, and thus, have a greater probability of being diagnosed with hyperlipidemia and receiving statins.[413,414] In this population, this may be especially true for patients under the age of 50 and needs further investigation.

A higher percent of Whites (41.2) received PIMs than other ethnic groups. Also, there were fewer Hispanics in the statin interacter group (27.2%) than the statin user group (33.6%). There is no reason to believe that there should be differences among ethnic groups when receiving statins and PIMs concurrently.

Objective 6: **To describe demographic characteristics of study population based on presence or absence of myopathy.**

More females than males had myopathy in both cohorts. This is consistent with the ACC/AHA/NHBLI clinical advisory on the use and safety of statins which has listed being female as one of the risk factors of myopathy.[415] In the current study, whether being female is associated with the risk of myopathy will be discussed later on.

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[413] Nau DP, Mallya U. Sex disparity in the management of dyslipidemia among patients with type 2 diabetes mellitus in a managed care organization. *Am J Manag Care* 2005;11:69-73.
[414] Roe CM, McNamara AM, Motheral BR. Gender- and age-related prescription drug use patterns. *Ann Pharmacother* 2002;36:30-9.
[415] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

In the statin user group, the mean age was similar for patients experiencing myopathy (50.3 years) and those without myopathy (51.1 years). However, in the statin interacter group, patients having myopathy were older (54.0 years) than those without myopathy (51.3 years). Increasing age is one of the risk factors of myopathy[416] and receiving PIMs may further increase the risk of myopathy. The association of age and risk of myopathy is discussed later in objective nine.

In both cohorts, more whites experienced myopathy than the other ethnic groups. In the statin user group, fewer Hispanics (28.6%) experienced myopathy than those without myopathy (33.5%). However, for the statin interacter group, more Hispanics (29.7%) had myopathy than those without myopathy (27.2%). This means being Hispanic and receiving PIMs with statins may further increase the probability of experiencing myopathy. More research needs to be done to understand the role of ethnicity in developing myopathy.

FACTORS ASSOCIATED WITH RECEIPT OF POTENTIALLY INTERACTING MEDICATIONS WITH STATINS

Objective four addressed identification of factors associated with receipt of PIMs with statins. A total of 3,005 patients received PIMs. This group was compared with the 5,817 patients who never received PIMs. Logistic regression analysis was used to identify risk factors associated with receiving PIMs and statins together. The risk factors included demographic characteristics of patients (age, gender, and ethnicity), presence of

[416] Ibid.

comorbidities and type and dose of statin used. Physician specialty was excluded from the analysis due to missing data.

Demographic factors

Three patient-related factors included in the analysis were age, gender, and ethnicity. Increasing age was associated with lower odds of receiving PIMs with statins (OR: 0.995; 95% CI: 0.990 – 0.999). Even though the result was statistically significant, as seen from 95% CI values, the difference was only minimal. Therefore, clinically it may be safe to say that age had no effect on the odds of receiving PIMs. This result may be counterintuitive as increasing age is associated with increased morbidity and therefore ,increased use of PIMs with statins. However, this study did not include patients above the age of 65 years and therefore the effect may be minimal.

Females had 1.5 (95% CI: 1.399–1.686) higher odds of receiving PIMs than males. As mentioned earlier, almost half the PIMs received in this study included antibiotics and antifungals, which were used primarily for conditions in females such as vaginal infections. Therefore, females may have higher odds of receiving PIMs with statins than males.

There was no statistically significant difference in the odds of receiving PIMs among different ethnic groups, except Hispanics. Hispanics had lower odds (OR: 0.755; 95% CI: 0.676 – 0.842) of receiving PIMs than Whites. It is unknown as to why this difference exists between Hispanics and Whites. This may be an area of future research.

Comorbidities

The number of comorbidities was included as a health-related risk factor in the logistic regression analysis to determine if the number of comorbidities was associated with receipt of PIMs. The list of comorbidities included was as listed in Table 2.6 in Chapter 2.

The odds of receiving PIMs with statins increased with an increasing number of comorbidities (OR: 1.427; 95% CI: 1.355-1.502). This finding is not surprising as one or more drugs may be prescribed to manage comorbidities that are diagnosed; this increases the odds of receiving PIMs with statins. Previous research has revealed that certain diagnoses are highly correlated with specific drug therapies that are known to interact with statins and given concurrently with statins.[417] Given the fact that close to 41% of population had at least one comorbidity in this study, it can be expected that the odds of receipt of PIMs with statins significantly increases with increasing comorbidities. The consequence of receiving PIMs with statins to manage other comorbidities may be a greater likelihood of experiencing an adverse event. It has been suggested that the possibility of interactions increases sharply with polypharmacy.[418,419] Physicians and pharmacists should be very cautious about managing patients with multiple comorbidities and should weigh the risks and benefits before prescribing/dispensing PIMs with statins.

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[417] Ratz Bravo AE, Tchambaz L, Krahenbuhl-Melcher A, et al. Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. *Drug Saf* 2005;28:263-75.

[418] Bottorf M. Safety and statins: Pharmacologic and clinical perspective. *Am J Manag Care* 2004;4:S30-S37.

[419] Williams D, Feely J. Underreporting of adverse drug reactions: attitudes of Irish doctors. *Ir J Med Sci* 1999;168:257-61.

Statin-related factors

The type and dose of statin used may be an important factor based on which a PIM may or may not be prescribed. The pharmacokinetic properties of drugs such as dose of drugs and routes of elimination play a very important role in drug interactions.[420] The pharmacokinetic properties of statins are different. The two important properties that differ are solubility and elimination of statins.[421,422] It is important to understand these differences as they may have clinical consequences. If physicians/pharmacists are aware of these subtle differences between statins, it may influence their decisions and consequently the receipt of PIMs with statins.

Patients receiving high doses of statins had lower odds of receiving of PIMs (OR: 0.967; 95% CI: 0.867 – 1.078) when compared with patients receiving low doses of statins; however, this result was not statistically significant. This result is not surprising as the ACC/AHA/NHBLI advisory on clinical use and safety of statins suggests that receiving PIMs with higher doses of statins increases the likelihood of myopathy.[423] Therefore, it can be expected that patients would receive PIMs more with lower doses of statins than with higher doses of statins. This indicates that there may be awareness among physicians/pharmacists to avoid prescribing/dispensing PIMs with high doses of statins. The consequence of statin dose on myopathy is discussed further in objective nine.

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[420] Hansten PD. Understanding drug-drug interactions. *Science & Medicine* 1998;5:16-25.
[421] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* 2005;19:117-25.
[422] Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002;41:343-70.
[423] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

All statins had lower odds of receiving PIMs when compared to pravastatin. However, this result was only statistically significant in patients using simvastatin. Pravastatin was used as the reference group as this is the only statin that is not metabolized by the CYP450 isoenzyme system. Specifically, simvastatin had 0.83 times lower of odds of receiving PIMs (95% CI: 0.712-0.973) as compared to pravastatin. This may be because simvastatin is metabolized by the CYP450 isoenzyme system and has higher likelihood of drug interaction than pravastatin which has carrier-mediated uptake in the liver making them less toxic.[424] Therefore, simvastatin had lower odds of receiving PIMs as the risk of drug interaction is higher than pravastatin. Similarly all other statins are also metabolized by CYP450 isoenzyme system[425] and therefore, have a higher likelihood of drug interaction with PIMs and therefore, lower odds of receiving PIMs with these statins. These results were consistent with one study in which pravastatin users received the highest percent of PIMs along with it compared to other statins.[426] However, these results contrast with those of another study where patients on simvastatin and atorvastatin had higher odds of receiving PIMs than pravastatin.[427] One explanation for this difference could be the time periods selected for the three studies. In the study by Etemad et al.,[428] the study period was around the withdrawal of cerivastatin. At that time, physicians may not have been very cautious about prescribing PIMs with statins.

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[424] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* 2005;19:117-25.
[425] Ibid.
[426] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[427] Etemad LR, Fairchild C, Waldeck R. *Prevalence and cost implications of potential interactions with statin medications in a managed care population.* ISPOR Ninth Annual International Meeting 2004. Washington, D.C.
[428] Ibid.

However, the current study as well as the study by Cziarky and colleagues[429] extended the study period two to three years before and after the withdrawal of cerivastatin. As a result, the physicians/pharmacists may have been more aware of the risks of prescribing PIMs with statins, due to the withdrawal of cerivastatin. Therefore, the odds of receiving PIMs were lower for all statins in this study when compared with pravastatin.

INCIDENCE OF MYOPATHY

The 8,822 study subjects were followed for an average of 3.9 months (S.D. = 2.1 months). During the study period, 113 patients (1.2%) developed new cases of myopathy. These results are consistent with those in clinical trials where the incidences of myopathy, mild or severe, have been reported between 0.1% and 5% depending on the dose and type of statin.[430,431] However, this study included patients who used PIMs with statins; therefore the estimated overall risk may be higher than in clinical trials.

A total of 8,822 persons contributed 35,022 person-months or 2,878 person-years of monotherapy. The total cases of myopathy in this study were 113 corresponding to an incidence rate of 0.32 per 100 person-months or 3.9 per 100 person-years. The overall incidence rate for myopathy was much higher than reported in previous studies. Gaist et al.[432] reported an incidence rate 0.023 per 100 person-years for myopathy while a study

[429] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[430] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[431] Bays H. Statin safety: an overview and assessment of the data-2005. *Am J Cardiol* 2006;97:S6-S26.
[432] Gaist D, Garcia Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565-9.

conducted in the US reported an incidence rate of 0.0044 per 100 person-years.[433] However, these incidences were only for patients who used statins by themselves. This study included patients who used statins with and without PIMs. Therefore, the overall incidence of myopathy may be higher than those reported in previous studies.

Incidence density was calculated for the statin user and statin interacter groups separately. Statin interacters had a higher incidence density (0.54 per 100 person-months or 6.5 per 100 person-years) as compared to statin users (0.21 per 100 person-months or 2.5 per 100 person-years). These results were compared to three other studies which examined the incidence rates for patients using only statins. The incidence rates were 0.023 per 100 person-years,[434] 0.0044 per 100 person-years[435] and 0.026 per 100 person-years.[436] These numbers are much lower than the incidence rate estimated for patients using statins in the current study (2.5 per 100 person-years). This difference may be because the study conducted on the US population by Graham and colleagues[437] and Cziarky and researchers[438] included only hospitalized cases of myopathy; whereas the current study included cases of myopathy that were diagnosed in hospitals, physicians' office as well as outpatient departments. Myopathy cases may be diagnosed at physicians' office and may not always require hospitalization. The cases of myopathy

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[433] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[434] Gaist D, Garcia Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565-9.
[435] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[436] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[437] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[438] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.

that do require hospitalization are probably the more severe forms of myopathy resulting in rhabdomyolysis.

The incidence density for statin interacters was 6.5 per 100 person-years. Data is sparse on the incidence of myopathy when patients use statins with PIMs. Graham and colleagues estimated the incidence of myopathy in patients using statins and fibrates at 0.0598 per 100 person-years.[439] The risk for myopathy was approximately 12 times higher in patients using statins and fibrates compared to those using statins by themselves. In the current study, which also included other PIMs besides fibrates, the risk for myopathy for statin interacters was approximately twice that for statin users. In another study, the risk of myopathy was six times higher in patients using statins and PIMs concurrently.[440] Thus, even though there is limited information on absolute incidence estimates for myopathy in statin interacters, the trends were very similar in the three known studies i.e. there appears to be higher risk for myopathy in patients using statins and PIMs than in those who use statins by themselves. The odds of myopathy associated with statins and PIMs will be discussed in detail later.

TIME TO DEVELOPMENT OF MYOPATHY

Objective 7 aimed at describing the time to development of myopathy for statin user and statin interacter group. The mean days of "survival" without myopathy was 115 days (S.E.: 1.19) for the statin interacter group and 120 days (S.E.: 0.81) for the statin

[439] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[440] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.

user group (Standard Error was reported in the output instead of Standard Deviation). This means that patients in the statin interacter group experienced myopathy earlier than patients in the statin user group. Graham and colleagues estimated the mean time to onset of myopathy for statin-fibrate combination therapy (32 days) which was lower than for patients using statins by themselves (348 days).[441]

There was a statistically significant difference in the probability of survival times between the two groups ($\chi 2 = 10.77$; $df = 1$; $p < 0.05$). This difference was largest at the start of observation period. The probability of survival at the end of one month was 0.99 for the statin user group and 0.88 for the statin interacter group. However, this difference decreased later in the follow-up period. At the end of follow-up period, the difference in probability of survival times was only minimal between the statin interacter (0.42) and statin user groups (0.45). This means patients using statins and PIMs concurrently developed myopathy faster than patients using statins by themselves; this is especially true at the start of therapy. This result was not surprising as concurrent use of PIMs with statins increases the blood levels of statins due to inhibition of metabolism of statins by PIMs, increasing the risk of myopathy.[442,443] However, it is not clear why the risk is greater at the start of therapy and decreased later on. More research needs to be conducted to determine why some patients experience myopathy early whereas some patients experience myopathy later.

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[441] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[442] Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol* 2006;97:S27-31.
[443] Bottorf M. Safety and statins: Pharmacologic and clinical perspective. *Am J Manag Care* 2004;4:S30-S37.

RISK OF MYOPATHY AND USE OF STATINS AND POTENTIALLY INTERACTING MEDICATIONS

The focus of objective eight was to assess the relationship between the development of myopathy and use of PIMs with statins. Logistic regression analysis was used to determine the odds of myopathy in patients using statins and PIMs, while controlling for other risk factors. The presence or absence of myopathy was the dependent variable and whether or not a patient received a PIM with statin was the independent variable. Other independent variables that were controlled for were age, gender, ethnicity, presence of diabetes, number of co-morbidities, type and dose of statin and duration of statin use.

Logistic regression analysis results revealed that the model had an acceptable fit based on global chi-square test ($\chi^2 = 61.2$; df = 13; $p < 0.0001$) and the Hosmer and Lemeshow statistic ($\chi^2 = 15.1$; df = 8; $p > 0.05$). The odds of developing myopathy were significantly higher for patients using statins and PIMs compared to patients using statins without PIMs. Specifically, statin interacters had 2. 7 (95% CI: 1.83–4.03) times greater odds of developing myopathy than statin users. These results were consistent with a previous study that reported a higher risk of myopathy in patients using statins and PIMs (RR: 6.01; 95% CI: 2.08–17.38) than those using statins alone.[444] However, the risk was much higher in that study than in the current study. One explanation may be that the previous study included drugs such as cyclosporine and HIV protease inhibitors which

[444] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.

were excluded from the current study. No other known study has compared the risk of myopathy in patients taking statins and PIMs concurrently.

Sub-group analysis to determine risk of myopathy for each category of potentially interacting medication used with statins

To determine the risk of myopathy with each type of PIM sub-group analyses were conducted. First, a chi-square analysis was conducted to determine if there were differences between groups. If there were significant differences and the sample size was large enough, then a logistic regression analysis was conducted to determine the odds of myopathy for each type of PIM used with statins. Table 4.2 provides information on the results of the chi-square analysis.

Table 4.2: Results of chi-square analysis of difference in myopathy cases between statin user group and each type of PIM used with statin

PIM[a] used[b]	Number of Patients	Myopathy Cases	χ^2	d.f.	p-value
Fibrates[c]	379	14	28.74[h]	1	<0.0001*
Calcium Channel Blocker[d]	879	18	11.20	1	0.0008*
Antidepressants[e]	90	4	12.93[h]	1	0.0003*
Macrolide Antibiotics[f]	1,225	22	9.21	1	0.002*
Azole Antifungals[g]	308	5	2.04[h]	1	0.15

* $p < 0.05$
a. PIM – Potentially Interacting Medication
b. The comparator group was statin user group with a total of 5,817 patients and 49 cases of myopathy
c. Fibrates include gemfibrozil and fenofibrate
d. Calcium Channel Blockers include diltiazem and verpamil
e. Antidepressant include nefazodone
f. Macrolide antibiotics include erythromycin, clarithromycin, and azithromycin
g. Azole Antifungals include fluconazole, ketoconazole and itraconazole
h. 25% of the cells have expected counts less than 5. Chi-Square may not be a valid test

As seen from Table 4.2, there was no statistically significant difference in the number of myopathy cases between the statin user group and patients using statins and azole antifungals concurrently. A chi-square analysis could not be conducted on patients using nicotinic acid and amiodarone due to small cell sizes. However, data from clinical trials have reported no cases of myopathy with the use of statins and niacin.[445,446] Similarly, data from clinical trials have not reported any cases of myopathy with the use of amiodarone and low doses of statins.[447] The patient using amiodarone who experienced myopathy in this study was using 10 mg atorvastatin. Very few patients

[445] Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583-92.
[446] Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003;163:553-64.
[447] Zocor. (simvastatin) [packcage insert]. Whitehouse Station, NJ: Merck & Co. Inc.; 2005.

were taking niacin or amiodarone in this study. A larger study with more patients may be warranted to have conclusive results about the risk of myopathy and use of niacin or amiodarone with statins.

Logistic regression analysis was done on other categories of PIMs to determine the odds of myopathy. Table 4.3 provides data on the results of logistic regression results for each category of PIM used with statins. The independent variables controlled for were age, gender, ethnicity, diabetes, number of comorbidities, type and dose of statin, and duration of statin use.

Table 4.3: Logistic regression analyses results to determine the odds of myopathy in patients using various PIMs and statins, concurrently

PIM[a] Used[b]	Parameter Estimate	Standard Error	Wald χ^2	df	p-value	Odds Ratio	95% Confidence Interval for Odds Ratio	
							Lower	Upper
Fibrates[c]	1.561	0.325	23.111	1	<0.0001*	4.763	2.521	9.000
Calcium Channel Blocker[d]	0.811	0.289	7.851	1	0.005*	2.251	1.276	3.967
Antidepressants[e]	1.715	0.550	9.720	1	0.002*	5.558	1.891	16.336
Macrolide Antibiotics[f]	0.951	0.289	10.821	1	0.001*	2.588	1.469	4.560
Azole Antifungals[g]	0.947	0.498	3.615	1	0.057	2.579	0.971	6.849

* $p < 0.05$

a. PIM – Potentially Interacting Medication
b. Reference category is statin user group
c. Fibrates include gemfibrozil and fenofibrate
d. Calcium Channel Blockers include diltiazem and verpamil
e. Antidepressant include nefazodone
f. Macrolide antibiotics include erythromycin, clarithromycin, and azithromycin
g. Azole Antifungals include fluconazole, ketoconazole and itraconazole

As seen from Table 4.3, using nefazodone and statins concurrently had the highest odds of developing myopathy, followed by patients using statins and fibrates together. Statistically, use of azole antifungals with statins had no difference in odds of developing myopathy as compared to statin users. The next section discusses each of these results in light of the current literature.

Risk of myopathy associated with use of statins and fibrates

The odds of developing myopathy was 4.7 times (95% CI: 2.521–9.000) higher in patients using statins and fibrates than those using statins by themselves. Graham and colleagues estimated the risk of myopathy to be 12 times greater in statin-fibrate combination therapy than statin monotherapy.[448] Another study estimated the risk of myopathy to be 0.84 for statin-gemfibrozil combination therapy and 1.84 for statin-fenofibrate combination therapy when compared with statin monotherapy; however, these results were not statistically significant.[449] These results were not surprising given the fact the both statins and fibrates are independently associated with the risk of myopathy.[450,451] Therefore, both drugs together increase the risk of myopathy. In addition to a pharmacodynamic reaction, there appears to be a pharmacokinetic reaction

[448] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[449] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[450] Birjmohun RS, Hutten BA, Kastelein JJ, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2005;45:185-97.
[451] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681-90.

occurring between statins and fibrates.[452] The results of this study are consistent with the physiologic process involved in statin-fibrate drug interaction as well as other known epidemiological studies.

Risk of myopathy associated with the use of statins and calcium channel blockers

There was a statistically significant difference in the odds of developing myopathy in patients using statins and calcium channel blockers (CCBs) as compared to patients using statins by themselves. Specifically, the odds of developing myopathy was 2.25 (95% CI: 1.276 - 3.967) times higher in patients using statins and CCBs concurrently than those using statins by themselves.

The body of evidence regarding the effect of use of statins and CCBs on risk of myopathy is very limited. In two clinical trials, the 4S and HPS trials, approximately 4,000 patients were taking a calcium channel blocker with statins; however, there was only one case of myopathy after four years of therapy.[453,454] This suggests that there is a low risk of myopathy with the use of statins and calcium channel blockers. However, there have been at least six case reports of rhabdomyolysis reported with the use of statins and calcium channel blockers in real world.[455,456,457] This is not surprising as

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[452] Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol* 2006;97:S27-31.
[453] Pedersen TR, Berg K, Cook TJ, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1996;156:2085-92.
[454] Gruer PJK, Vega JM, Mercuri MF, et al. Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. *Am J Cardiol* 1999;84:811-815.
[455] Lewin JJ, 3rd, Nappi JM, Taylor MH. Rhabdomyolysis with concurrent atorvastatin and diltiazem. *Ann Pharmacother* 2002;36:1546-9.
[456] Gladding P, Pilmore H, Edwards C. Potentially fatal interaction between diltiazem and statins. *Ann Intern Med* 2004;140:W31.
[457] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288-95.

pharmacokinetic studies have shown that both verapamil and dilitazem increase the mean peak serum concentration of statins (approximately three times).[458,459] CCBs inhibit the CYP 450 isoenzyme metabolism of statins increasing the blood of levels of statins.[460] This increases the risk of myopathy. The current study reinstates the fact that there is an increased risk of myopathy associated with the use of statins and CCBs. Health care professionals need to be aware and cautious when using these two drugs together.

Risk of myopathy associated with the use of statins and nefazodone

Antidepressant drugs such as fluxoetine, fluvoxamine, sertraline, and nefazodone inhibit CYP3A isoenzymes and should be used cautiously with statins.[461] The clinical advisory on clinical use and safety of statins has listed nefazodone as the only drug that may increase the risk of myopathy.[462] This is because case-reports of myopathy have only been reported with the use of statins and nefazodone. For this reason, only nefazodone was included in this study.

The odds of developing myopathy was 5.5 (95% CI: 1.89 – 16.36) times higher in patients using statins and nefazodone than those using statins by themselves. In fact, among all the statin and PIMs combinations, concurrent use of statin and nefazodone had the highest odds of developing myopathy. No other known study has evaluated the risk

[458] Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004;94:1140-6.
[459] Mousa O, Brater DC, Sunblad KJ, et al. The interaction of diltiazem with simvastatin. *Clin Pharmacol Ther* 2000;67:267-74.
[460] Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004;94:1140-6.
[461] Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 1996;153:311-20.
[462] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

of myopathy in patients using statins and nefazodone. However, pharmacokinetic studies have revealed an increase in concentration of atorvastatin and simvastatin by 3.4-fold and 20-fold respectively.[463] This study further emphasizes that the data seen in the pharmacokinetic study may be translated into increased risk of myopathy when statins and nefazodone are taken together. More studies need to be conducted to further support the results found in the current study. Nevertheless, physicians need to be aware when prescribing these drugs together.

Risk of myopathy with statins and macrolide antibiotics

Macrolide antibiotics increase the blood levels of statins by inhibiting statin metabolism.[464] This increases the risk of myopathy. The current study results were consistent with the proposed mechanism of increased risk of myopathy when both drugs are taken together. The odds of developing myopathy was 2.5 (95% CI: 1.46 – 4.56) times higher for patients using statins and macrolide antibiotics concurrently than those using statins alone. No other known study has evaluated the risk of myopathy in patients using statins and macrolide antibiotics. However, pharmacokinetic studies have revealed that macrolide antibiotics significantly increase the concentration of statins two- to eight-fold depending on type and dose of statin used.[465,466] Similarly, in a review of the FDA database of adverse events, 42 cases of rhabdomyolysis were associated with the use of

[463] Serzone (nefazodone). [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2004.
[464] Lee AJ, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. *Ann Pharmacother* 2001;35:26-31.
[465] Amsden GW, Kuye O, Wei GC. A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol* 2002;42:444-49.
[466] Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004;94:1140-6.

statins and macrolide antibiotics.[467] Given this information, it was not surprising to find an increased risk of myopathy associated with use of statins and macrolide antibiotics. Physicians/pharmacists need to be aware of this interaction, and may be stop statins for a short interval when patients are using macrolide antibiotics.[468]

Risk of myopathy associated with the use of statins and azole antifungals

The odds of developing myopathy was higher (OR: 2.579; 95% CI: 0.971-6.849) in patients using statins and azole antifungals as compared to those using statins by themselves; however, this result was not statistically significant. The mechanism of drug interaction is similar to other PIMs i.e. inhibition of CYP450 isoenzyme system increasing the blood levels of statins; thereby, increasing risk of myopathy.[469] Pharmacokinetic studies evaluating the effect of azole antifungals on statins have shown on an average two- to thirteen-fold increases in concentrations of statins, based on type of statin used.[470,471,472] Case reports of rhabdomyolysis have been reported with the use of statins and azole antifungals; most of these patients were old with multiple comorbidities.[473,474] Therefore, the results of this study are supported by current

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[467] Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;36:288-95.
[468] Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;97:S52-60.
[469] Shaukat A, Benekli M, Vladutiu GD, et al. Simvastatin-Fluconazole Causing Rhabdomyolysis. *Ann Pharmacother* 2003;37:1032-1035.
[470] Neuvonen PJ, Kantola T, Kivisto KT. Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clin Pharmacol Ther* 1998;63:332-41.
[471] Kantola T, Kivisto KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther* 1998;64:58-65.
[472] Kantola T, Backman JT, Niemi M, et al. Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. *Eur J Clin Pharmacol* 2000;56:225-9.
[473] Shaukat A, Benekli M, Vladutiu GD, et al. Simvastatin-Fluconazole Causing Rhabdomyolysis. *Ann Pharmacother* 2003;37:1032-1035.

literature. However, more research needs to be conducted to support the results of this study. Caution should be exercised when using these drugs together.

In summary, the results of the current study show that there is an increased risk of myopathy when using statins and PIMs together. This risk is varied for each class of PIM used with statins, with the highest risk of myopathy being for patients using nefazodone and fibrates with statins. There is some information on risk of myopathy in patients using statins and PIMs, and the current study further supports other research findings. More research needs to be conducted to study the effect of use of statins and PIMs on risk of myopathy. This will help health care professionals better manage patients receiving PIMs.

RISK FACTORS ASSOCIATED WITH MYOPATHY

The last and final objective of this study was to determine the risk factors associated with myopathy. Some of the risk factors listed by the AHA/ACC/NHBLI clinical advisory on clinical use and safety of statins include increasing age, female, increased physical activity, small body size, presence of comorbid conditions and dose of statin used.[475] Data were not available on all the risk factors. However, the effects of the following risk factors on odds of developing myopathy were evaluated: age, gender, ethnicity, presence of diabetes, number of comorbidities, statins characteristics and PIM

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[474] Horn M. Coadministration of itraconazole with hypolipidemic agents may induce rhabdomyolysis in healthy individuals. *Arch Dermatol* 1996;132:1254.

[475] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

characteristics. Logistic regression analyses were utilized to address this objective. Two models were run: one on the entire population and a second only on statin interacters to determine the PIM characteristics that are associated with myopathy. The results for each risk factor are discussed in the next section, comparing and contrasting the results with available literature.

Age

Increasing age had higher odds (OR: 1.009; 95% CI: 0.988-1.030) of developing myopathy; however, the results were not statistically significant. Previous studies have reported increased risk of myopathy in patients aged 65 years and above, with the risk being 1.8 to 5.0 times higher in older patients than in younger patients.[476,477] Increasing age is known to affect muscles and thus increasing risk of myopathy.[478] However in this study age was not statistically significant.

Gender

The ACC/AHA/NHBLI clinical advisory of safety of statins suggests that females have a higher risk for myopathy than males.[479] The current study reported no statistically significant difference (OR: 1.317; 95% CI: 0.881-1.970) between males and females in odds of developing myopathy. These results are consistent with two studies that assessed

[476] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[477] Gaist D, Garcia Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565-9.
[478] Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004;116:408-16.
[479] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

the association between gender and risk of myopathy. These studies also reported no difference in risk of myopathy between males and females.[480,481] Increasing evidence appears to be pointing in the direction of no difference in the risk of myopathy based on gender.

Ethnicity/Race

There was no difference in the odds of myopathy based on ethnicity/race. Whites had higher odds of myopathy as compared to all other ethnicities but the results were not statistically significant. There is an assumption made that difference in genetic makeup of various ethnicities/races may affect the risk of myopathy. However, no known epidemiological studies have evaluated the association between the risk of myopathy and ethnicity/race. One pharmacokinetic study conducted on rosuvastatin revealed a greater risk of myopathy in Asians than other sub-populations.[482] There were very few Asians in the current study. More research needs to be conducted to understand the association of ethnicity and risk of myopathy.

Diabetes

It has been postulated that patients having diabetes have reduced drug metabolism which increases the concentrations of statins in blood thereby increasing the risk of

[480] Gaist D, Garcia Rodriguez LA, Huerta C, et al. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 2001;12:565-9.
[481] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[482] Crestor (rosuvastatin). Wilmington, DE: AstraZeneca Pharmaceuticals; 2005.

myopathy.[483] In the current study, the odds of myopathy were higher (OR: 1.151; 95% CI: 0.783-1.692) for patients having diabetes than those without diabetes; however, the results were not statistically significant. Similar results were observed in another study where the risk of myopathy was 1.40 times higher in patients with diabetes, but the results were not statistically significant.[484] Graham and colleagues also reported increased risk of myopathy (RR: 2.9; 95% CI: 0.7- 11.8) in patients with diabetes; however, the results were not statistically significant.[485] According to ATP III guidelines, patients with diabetes have the same risk of developing cardiovascular disease as patients who have cardiovascular diseases.[486] Therefore, it is important to manage hyperlipidemia in patients with diabetes. Health care professionals should closely monitor patients with diabetes using statins and be aware of the risk of myopathy in these patients.

Number of co-morbidities

Presence of comorbid conditions may increase the risk of myopathy. It is known that renal insufficiency, hepatic dysfunction and hypothyroidism have risk of myopathy independent of statin use due to polypharmacy and altered drug metabolism.[487,488]

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[483] Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;289:1681-90.
[484] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[485] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[486] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
[487] Sica DA, Gehr TW. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and rhabdomyolysis: considerations in the renal failure patient. *Curr Opin Nephrol Hypertens* 2002;11:123-33.
[488] Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004;116:408-16.

Adding statin therapy further increases this risk. These patients were excluded from the current study. However, the risk of myopathy in presence of other comorbid conditions is not known. In addition, the presence of comorbid conditions may increase the receipt of PIMs to manage these conditions which further increase risk of myopathy. This study results revealed that the odds of receiving PIMs increases with increasing number of comorbidities. Previous research has suggested the probability of interactions increases sharply with polypharmacy, which in turn, is related to number of comorbidities.[489,490] This increases the risk of adverse events like myopathy. Therefore it is important to assess the association between number of comorbidities and risk of myopathy.

The odds of myopathy increased 1.3 times (95%CI: 1.159-1.637) with increasing number of comorbidities. No other known study has evaluated the association between myopathy and comorbidities. However, one study showed five times (95% CI: 2.42 – 10.85) increased risk of myopathy in patients with hypertension.[491] These results are not surprising as patients with comorbidities may be taking multiple medications to manage comorbidities. Taking multiple medications with statins is listed as one of the risk factors of statin-associated myopathy.[492] This may be because polypharmacy results in altered statin metabolism or inhibition of statin metabolism.[493] This may increase blood levels of

[489] Bottorf M. Safety and statins: Pharmacologic and clinical perspective. *Am J Manag Care* 2004;4:S30-S37.
[490] Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol* 2006;97:S27-31.
[491] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[492] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.
[493] Sica DA, Gehr TW. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and rhabdomyolysis: considerations in the renal failure patient. *Curr Opin Nephrol Hypertens* 2002;11:123-33.

statins increasing risk of myopathy. Physicians/pharmacists need to be more aware of patients with multiple comorbidities and closely monitor these patients.

Statin characteristics

Three factors related to statin use were included in this study. These were type of statin used, dose of statin used and duration of statin use before end of observation period. The discussion of each of the factors follows.

Type of statin

The odds of myopathy were higher for atorvastatin (OR: 1.311; 95% CI: 0.725-2.372) and simvastatin (OR: 1.071; 95% CI: 0.549-2.091) as compared to pravastatin whereas lower for other statins (OR: 0.388; 95% CI: 0.076-1.497); however, none of these results were statistically significant. These results are consistent with the study conducted by Graham and colleagues where the researchers found statistically indistinguishable rates of incidences of rhabdomyolysis among statins, even though the incidence rates of rhabdomyolysis were higher among atorvastatin and simvastatin users as compared to pravastatin users.[494] In another study, simvastatin and fluvastatin had a higher risk of myopathy when compared with pravastatin; however, atorvastatin and lovastatin had a lower risk of myopathy than pravastatin.[495] Again, none of the results in that study were statistically significant. Even though the results of studies are

[494] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[495] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.

inconsistent, all three studies revealed that the risk of myopathy is similar among all statins. It is believed that the difference in the pharmacokinetic properties of statins may affect the risk of myopathy.[496,497] Due to a different metabolism mechanism of pravastatin as compared to other statins, it has the least potential of myopathy.[498] However, the current study as well as previous studies reveals that there are no statistically significant differences in risk of myopathy among statins.

Dose of statin

There was no statistically significant difference in the odds of myopathy (OR: 0.853; 95% CI: 0.545-1.333) based on whether a patient received lower or higher doses of statins. This is inconsistent with the current suggestions which states myopathy occurs more likely in patients with higher doses of statins and lower doses. Clinical trials have also shown that myopathy most likely occurs in higher doses of statins than lower doses. This is because higher the dose, greater the concentration of statin in blood and greater the risk of myopathy. It is not clear why these results were not obtained in the current study. One explanation may be grouping of doses of statins into just two categories, which was done based on efficacy of statins. For example, 10 mg of atorvastatin was grouped with 40 mg of pravastatin as at these doses both drugs had similar efficacy (Table 2.7). This may have resulted in grouping of high doses of one drug with lower

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[496] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* 2005;19:117-25.
[497] Bottorf M. Safety and statins: Pharmacologic and clinical perspective. *Am J Manag Care* 2004;4:S30-S37.
[498] Muscari A, Puddu GM, Puddu P. Lipid-lowering drugs: are adverse effects predictable and reversible? *Cardiology* 2002;97:115-21.

doses of another. Future studies should evaluate the association between dose of statins and myopathy for each statin separately to better understand the link between the two.

Duration of statin use

The odds of developing myopathy decreased (OR: 0.997; 95% CI: 0.995-0.999) with increasing duration of statin use. Even though the results are statistically significant, the confidence interval is so close to one that it is safe to say that clinically there may be no association between odds of myopathy and duration of statin use. In a review of the FDA database, the mean duration of statin use before experiencing myopathy varied from 10 days for fluvastatin to 309 days for atorvastatin.[499] The association between duration of statin use and myopathy is not well understood. This study supports slightly lowers odds of developing myopathy with increasing duration. This means that odds of developing myopathy is greater at the start of statin therapy and decreases as patient continues the therapy. This result is also supported by results of th survival analysis where more patients experienced myopathy at the start of observation period. More research needs to be conducted to understand why some patients experience myopathy at the start of statin therapy while others experience it later. However, based on the results of this study, patients should be monitored closely when they first start therapy.

[499] Chang JT, Staffa JA, Parks M, et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Saf* 2004;13:417-26.

Characteristics of potentially interacting medications

The risk of developing myopathy may be affected by characteristics of PIMs used with statins. It is known that PIMs increase the risk of myopathy; however, not much research has been done on characteristics of PIMs that are associated with myopathy. Therefore, this study analyzed the association between myopathy and PIM characteristics such as level of significance of drug interaction, whether PIM was received before or after the start of statin therapy and duration of PIM use before experiencing myopathy. Logistic regression analysis was conducted only on statin interacters to assess the link between myopathy and PIM characteristics. The next part discusses each of these factors in detail.

Level of significance of drug interaction

Based on type of PIM received with statins concurrently, the drug interaction was classified as follows: 1) Level 1- potentially life-threatening; 2) Level 2 - deterioration in patients' clinical status; or 3) Level 3 - causing moderate to minor side-effects.[500] The Level 1 drug interaction included fibrates, antidepressants and macrolide antibiotics, Level 2 drug interaction included calcium channel blockers and antifungals, and Level 3 drug interactions included nicotinic acid and amiodarone.

The results of this study showed that the odds of developing myopathy was lower for Level 2 (OR: 0.757; 95% CI: 0.416-1.376) and Level 3 (OR: 0.280; 95% CI: 0.037-2.145) significance of drug interaction as compared to Level 1; however, the results were

[500] Drug Interaction Facts. Wolters Kluwer Health, Inc, 2003-2005. Available at: http://www.efactsonline.com/Fac/servlet/MainPage. Accessed on: January 2005

not statistically significant. These results are surprising given the fact that drugs included in Level 1 such as fibrates are know to increase the risk of myopathy approximately 12 times than those without these medications.[501] It is not clear why differentiation based on Level of significance of drug interaction was not found; however, sub-group analysis based on type of PIM used revealed a difference in odds of myopathy based on type of PIM used.

Time of receipt of potentially interacting medications

Risk of myopathy may be associated with whether a patient received a PIM before or after the start of statin therapy. The assumption behind this association is if a patient is already on a PIM before start of statin therapy, the metabolism of the statin may be inhibited right from the start of therapy, increasing the risk of myopathy. However, if a patient receives a PIM after starting statin therapy, the effect of PIM on statin metabolism may be slower, and therefore, risk of myopathy may be lower. The current study revealed that there is no statistically significant difference in the odds of myopathy (OR: 1.272; 95% CI: 0.647-2.500) based on whether patient receives PIM before or after start of statin therapy. However, as discussed earlier, receipt of PIMs with statins has higher risk of myopathy than patients using statins by themselves.

[501] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.

Duration of PIM use

Duration of PIM use had no statistically significant association (OR: 0.997; 95% CI: 0.992-1.002) with the odds of developing of myopathy. No known previous studies have reported the association between two. The average duration of PIM use was 58 days. However, approximately 50% of patients received macrolide antibiotics or azole antifungals, which are used for shorter duration. In spite of this fact, patients using statins and PIMs seemed to have increased risk of myopathy. Thus it seems that short duration of PIM use may be as harmful as longer duration of PIM use. More research needs to be conducted on the association of duration of PIM use and risk of myopathy, especially PIMs used for a shorter duration of time.

STUDY LIMITATIONS

Some limitations of the study need to be pointed out before discussing the implications of this study. First of all, the results of current study are generalizable only to the Texas Medicaid population. The enrollment of patients into Medicaid is based on certain eligibility criteria and poverty levels. These criteria vary from state to state. Therefore, these results cannot be applicable to other state Medicaid programs as well as non-Medicaid programs.

The second limitation is related to the use of a claims database for an epidemiological study. The details of limitations of claims database are discussed in Appendix A. In brief, claims databases are subject to errors in coding, errors in data

entry and missing data as well as threats to construct validity when proxies are used for medical conditions.

The third limitation is lack of information on several variables that are associated with risk of myopathy. Texas Medicaid does not have information on several important lifestyle risk factors such as physical activity, body size, and consumption of grapefruit/alcohol. These factors increase the risk of myopathy; however, these factors could not be controlled for in this study. Also, laboratory data were not available to monitor creatine kinase levels, which is an indicator of myopathy. Therefore, the current study relied on ICD-9-CM codes for diagnosis of myopathy, which as discussed before, are subject to coding errors.

The fourth limitation is that the data in this study included only those prescriptions paid for by Texas Medicaid. There is a three prescription per month drug limit for some enrolled patients. It is possible that patients may have received medications from physicians' office or paid for medications themselves due to this limit. These prescriptions have not been captured in the current study. This may result in biased estimates in the current study. A more complete study would include all drugs used by the patient and not just those paid by Texas Medicaid.

The fifth limitation involves threats to internal validity. The most important of all is history. During the study time period of this study, cerivastatin was withdrawn due to deaths caused by rhabdomyolysis. Therefore, physicians may have been more careful with statins and monitored patients more closely for myopathy. As result of this, myopathy may have been over diagnosed leading to over estimation of risk of myopathy.

Also, there may be selection bias due to lack of randomly assigned groups. The statin interacter group may be more chronically ill than the statin user group increasing the likelihood of myopathy in that group.

Finally, due to multiple statistical tests, there could be the possibility of inflated type I errors. Also, the current study was designed to evaluate the association of risk of myopathy and use of statins with PIMs; however, it would be inappropriate to draw causal inferences from the current study. A controlled clinical trial or a prospective cohort study should be designed for causal inferences.

STUDY IMPLICATIONS AND FUTURE RESEARCH

This study aimed to help fill the gap in the literature related to risk of myopathy and use of statins with PIMs. The principal objective of this study was to assess the relationship between development of myopathy and use of statins with PIMs and identify the risk factors of myopathy. The results of the current study revealed the following:

1) The odds of myopathy increased two-fold in patients receiving statins and PIMs when compared with patients using statins by themselves. This risk was highest in patients using nefazodone, fibrates, and macrolide antibiotics.
2) Increasing age, being female, having diabetes, and using atorvastatin and simvastatin had higher odds of developing myopathy; however, the results were not statistically significant
3) The odds of myopathy increased 1.3 times with increasing number of comorbidities.

4) The odds of myopathy were greater when statin therapy was first started and gradually decreased after prolonged use.
5) There was no difference in the odds of myopathy based on ethnicity and dose of statins.

Previous research studies have shown similar results when conducting studies evaluating the association between statins and myopathy and risk factors.[502,503] However, these studies included only hospitalized cases of myopathy and did not evaluate the risk of myopathy with the concurrent use of statins and PIMs. The current study included all cases of myopathy including those being diagnosed in physicians' offices and outpatient departments and those related to the concurrent use of statins and PIMs. The ACC/AHA/NHBLI clinical advisory on clinical use and safety of statins has listed certain PIMs as increasing the risk for statin-associated myopathy.[504] Their recommendations were based primarily on case-reports and reports of adverse events to the FDA database. This study adds scientific evidence to their recommendations that use of PIMs with statins increases the risk of myopathy. Further sub-group analysis revealed that nefazodone and fibrates had the highest odds of developing myopathy. Future studies should be designed to determine the risk of each category of PIM used with statins to further confirm the results of the current study.

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[502] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[503] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-90.
[504] Pasternak RC, Smith SC, Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567-72.

In addition, the ACC/AHA/NHBLI clinical advisory on clinical use and safety of statins had identified a number of demographic, health-related and treatment-related factors that might increase the risk of myopathy. The most important factor that increased the risk of myopathy was number of comorbidities. This is not surprising considering patients with comorbidities may receive multiple medications and may have altered drug metabolism. Future studies should identify the comorbidities that increase the risk of myopathy.

The odds of myopathy decreased with increasing duration of statin use. These results are supported by survival analysis results where more patients experience myopathy at the start of therapy and this number slowly decreases. In spite of the current study results, there is insufficient evidence to conclude that myopathy occurs earlier in statin therapy than later. Future studies should identify factors that affect time to develop myopathy.

Increasing age was identified as one of the risk factors of myopathy. In the current study, the odds of myopathy increased with age; however, this result was not statistically significant. The present study did not include patients above the age of 65 years, due to lack information. More research is needed on patients aged 65 and older to determine what factors trigger myopathy in these patients.

Atorvastatin and simvastatin had higher odds of myopathy than pravastatin, even though the results were not statistically significant. Pravastatin has a different mechanism of metabolism than other statins, which decreases the risk of myopathy in patients using pravastatin. The current study did not study the effect of switching statins

on myopathy. Future research should be conducted on patients switching medications to better understand the role of different statins on risk of myopathy.

Based on the current study findings and the literature available on statin-associated myopathy, the following suggestions are made to the health care professionals:

1) Patients using statins and PIMs should be monitored closely. It is recommended that patients should stop statins for a short time when taking PIMs such as macrolide antibiotics or switch to pravastatin when using PIMs for long-term to decrease the risk of statin-associated myopathy.[505]
2) Patients should be monitored more closely for myopathy when they first start statin therapy as well as when they start using PIMs with statin therapy.
3) Patients having multiple comorbidities are more likely to experience myopathy. Physicians/pharmacist should be aware of these patients and appropriately manage all comorbidities to minimize the risk of adverse events.[506]
4) Patients receiving statin therapy should be counseled about risk of myopathy and be advised to report such cases to health care professionals.[507]
5) CK measurements are recommended in patients experiencing muscle symptoms or patients having risk factors such as renal insufficiency or hepatic dysfunction. However, pretreatment baseline CK measurements or those in asymptomatic patients are not required.[508,509]

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[505] Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;97:S52-60.
[506] Thompson PD, Clarkson PM, Rosenson RS. An assessment of statin safety by muscle experts. *Am J Cardiol* 2006;97:S69-76.
[507] McKenney JM, Davidson MH, Jacobson TA, et al. Final conclusions and recommendations of the national lipid association statin safety assessment task force. *Am J Cardiol* 2006;97:S89-94.
[508] Ibid.

CONCLUSION

This study showed that there is an increased risk of myopathy in patients using statins and certain PIMs. This is consistent with the finding of previous research which also showed an increased risk with concurrent use of statins and PIMs.[510] In addition, increasing number of comorbidities further increased the risk of myopathy. Recent guidelines recommend more aggressive treatment of elevated cholesterol levels.[511] This means there will be a substantial number of people who will receive statin therapy, of which many will have comorbidities and receive PIMs. Given this scenario, it will be the responsibility of health care professionals to appropriately monitor patients to prevent statin-associated myopathy. The benefits of statin therapy in reducing cardiovascular risk is tremendous. Vigilance and awareness on the part of health care professionals in understanding the risk factors and the role of PIMs related to myopathy can help patients obtain benefits of statin therapy without worrying about statin-associated myopathy.

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[509] Thompson PD, Clarkson PM, Rosenson RS. An assessment of statin safety by muscle experts. *Am J Cardiol* 2006;97:S69-76.
[510] Cziraky MJ, Willey VJ, McKenney JM, et al. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;97:S61-8.
[511] Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227-39.

APPENDIX A

ADVANTAGES AND DISADVANTAGES OF USING CLAIMS DATABASES

The proposed study used Texas Medicaid prescription and medical claims to meet the study goals. The use of databases for pharmacoepidemology studies has advantages and disadvantages. This section contains a brief discussion of the advantages and disadvantages for the use of claims databases. This discussion is based on reviews of use of databases for outcomes research and pharmacoepidemiology by Motheral and colleagues,[512,513] and Strom and colleagues.[514,515]

Advantages of using claims databases

1) Claims databases allow the evaluation of treatments in "real-life" situations such as effectiveness and safety of treatments in clinical practice settings.
2) Claims databases are large with information on a large number of patients. This allows epidemiological research even when the drug exposure or the disease of interest is uncommon.
3) Research using claims databases is less expensive and time consuming as compared to prospective studies or clinical trials.

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[512] Motheral BR, Fairman KA. The use of claims databases for outcomes research: rationale, challenges, and strategies. *Clin Ther* 1997;19:346-66.
[513] Motheral B, Brooks J, Clark MA, et al. A checklist for retrospective database studies--report of the ISPOR Task Force on Retrospective Databases. *Value Health* 2003;6:90-7.
[514] Strom BL. Data validity issues in using claims data. *Pharmacoepidemiol Drug Saf* 2001;10:389-92.
[515] Carson J, Wayne R, Strom BL. *Medicaid Databases*. In: Strom BL, ed. Pharmacoepidemiology. London: John Wiley & Sons, Ltd., 2000:307-24.

4) In a claims database, the data on exposure are not subject to recall or interviewer bias.
5) Claims database research allows linking of pharmacy claims with medical claims. This permits the examination of different aspects or providing health care including patient outcomes and health care cost and utilization.
6) Theoretically, databases are population-based. This allows calculation of incidence rates.
7) An advantage of the Medicaid database is overrepresentation of special populations such as women, children, and different ethnic groups. As these populations are underrepresented in clinical trials, information on different outcomes in these vulnerable populations is important.

Disadvantages of using claims database

1) The information available for a population in a certain claims database may not be generalizable to other populations. This is especially true for Medicaid populations because of specific characteristics of populations served by Medicaid.
2) Using claims databases for research poses a threat to construct validity. Construct validity refers to the degree to which a variable measures what it is meant to measure. For example, the use of a drug as a proxy for the presence of a medical condition can be misleading.
3) Using claims databases for research poses a threat to internal validity. Some examples include the following:

a. Using ICD-9-CM codes in database research may not always be reliable or valid. Under-coding or over-coding of diagnoses can occur that could result in study bias.
b. Misclassification of exposure could lead to bias in the study results.
c. Presence of confounding variables such as severity of illness can lead to biased results. Information on many important confounding variables are missing from Medicaid databases and hence cannot be controlled for in the study.

4) Eligibility changes to insurance programs such as Medicaid may cause patients to be terminated from the study. This may result in misinterpretation that the outcome of interest did not occur, when in reality, the patient was no longer a part of the study.
5) Medical claims for individuals above 65 years of age may be incomplete due to dual eligibility in Medicaid and Medicare programs.
6) Missing data such as those for prescription claims could be problematic especially when assessing prescription refill patterns since the apparent failure to refill prescriptions could be the results of missing claims rather than lack of patients' adherence.

APPENDIX B

ICD-9-CM CODES AND DRUGS USED FOR PATIENT SELECTION CRITERIA

Table B.1: Description of ICD-9-CM codes used to identify myopathy events

ICD-9-CM codes	Description
791.3	Myoglobinuria
359.4, 359.8, 359.9	Myopathy
729.1	Myositis
710.4	Polymyositis
728.9	Muscle Weakness
729.81, 729.82, 729.89	Musculoskeletal symptoms of the limbs
E942.2	Adverse effect from antihyperlipidemic agents

Table B.2: Description of ICD-9-CM codes used to identify renal insufficieny

ICD-9-CM codes	Description
585.1-585.6, 585.9	Chronic Kidney Disease
586	Renal failure, unspecified
593.9	Unspecified disorder of Kidney

Table B.3: Description of ICD-9-CM codes used to identify hepatic dysfunction

ICD-9-CM codes	Description
570	Acute and subacute necrosis of liver
571.xx	Chronic liver disease and cirrhosis
572.xx	Liver abscess and sequelae of chronic liver disease

Table B.4: Description of ICD-9-CM codes to identify hypothyroidism

ICD-9-CM codes	Description
243	Congenital Hypothyroidism
244.xx	Acquired Hypothyrodism

Table B.5: List of hypothyroid drugs

Name of Drug
Armour thyroid
Cytomel
Levo-T
Levotabs
Levothroid
Levothyroxine
Levoxyl
Synthroid
Thyrolar
Unithroid

Table B.6: Description of ICD-9-CM codes to identify HIV

ICD-9-CM codes	Description
042.x – 044.x	HIV infection

Table B.7 List of HIV drugs

Therapeutic Class	Brand Name	Generic Name
Nucleoside Reverse Transcriptase Inhibitors	Combivir	lamivudine and zidovudine
	Emtriva	FTC, emtricitabine
	Epivir	lamivudine, 3TC
	Epzicom	abacavir/ lamivudine
	Hivid	zalcitabine, ddC, dideoxycytidine
	Retrovir	zidovudine, AZT, azidothymidine, ZDV
	Trizivir	abacavir, zidovudine, and lamivudine
	Videx EC	enteric coated didanosine
	Videx	didanosine, ddI, dideoxyinosine
	Viread	tenofovir disoproxil fumarate
	Zerit	stavudine, d4T
	Ziagen	abacavir
Nonnucleoside Reverse Transcriptase Inhibitors	Rescriptor	delavirdine, DLV
	Sustiva	efavirenz
	Viramune	nevirapine, BI-RG-587
Protease Inhibitors	Agenerase	amprenavir
	Crixivan	indinavir, IDV, MK-639
	Fortovase	saquinavir
	Invirase	saquinavir mesylate, SQV
	Kaletra	lopinavir and ritonavir
	Norvir	ritonavir, ABT-538
	Reyataz	atazanavir sulfate
	Viracept	nelfinavir mesylate, NFV
Fusion Inhibitors	Fuzeon	enfuvirtide, T-20

APPENDIX C

PROPOSED METHODOLOGY FOR COHORT FORMATION AND STATISTICAL ANALYSES PLAN

The current section describes the methodology initially proposed for conducting the current study. However, this methodology was not followed. After data cleaning and assembling cohorts based on the initial proposed methodology a small number of patients were identified who were initially statin users and then switched cohorts after receipt of PIMs. A further analysis of these patients revealed that none of these patients had myopathy before receipt of PIMs. In order to obtain clean cohorts, it was decided to include these patients only in the statin interacter group. Therefore, only two clean groups were assembled without any overlapping of patients.

Cohort 1, the statin user

For the purpose of this study, a patient who receives a statin without any potentially interacting medication is defined as a **statin user**. A statin user can receive any other medications besides the list of potentially interacting medications listed in Table 2.1.

The index date for statin user will be defined as the date of first pharmacy claim for any statin starting from March 1, 1999. To include only new users of statins, the patient should not receive any statin medication six months prior to the first pharmacy claim. The patients will be followed until they experience myopathy, discontinue therapy

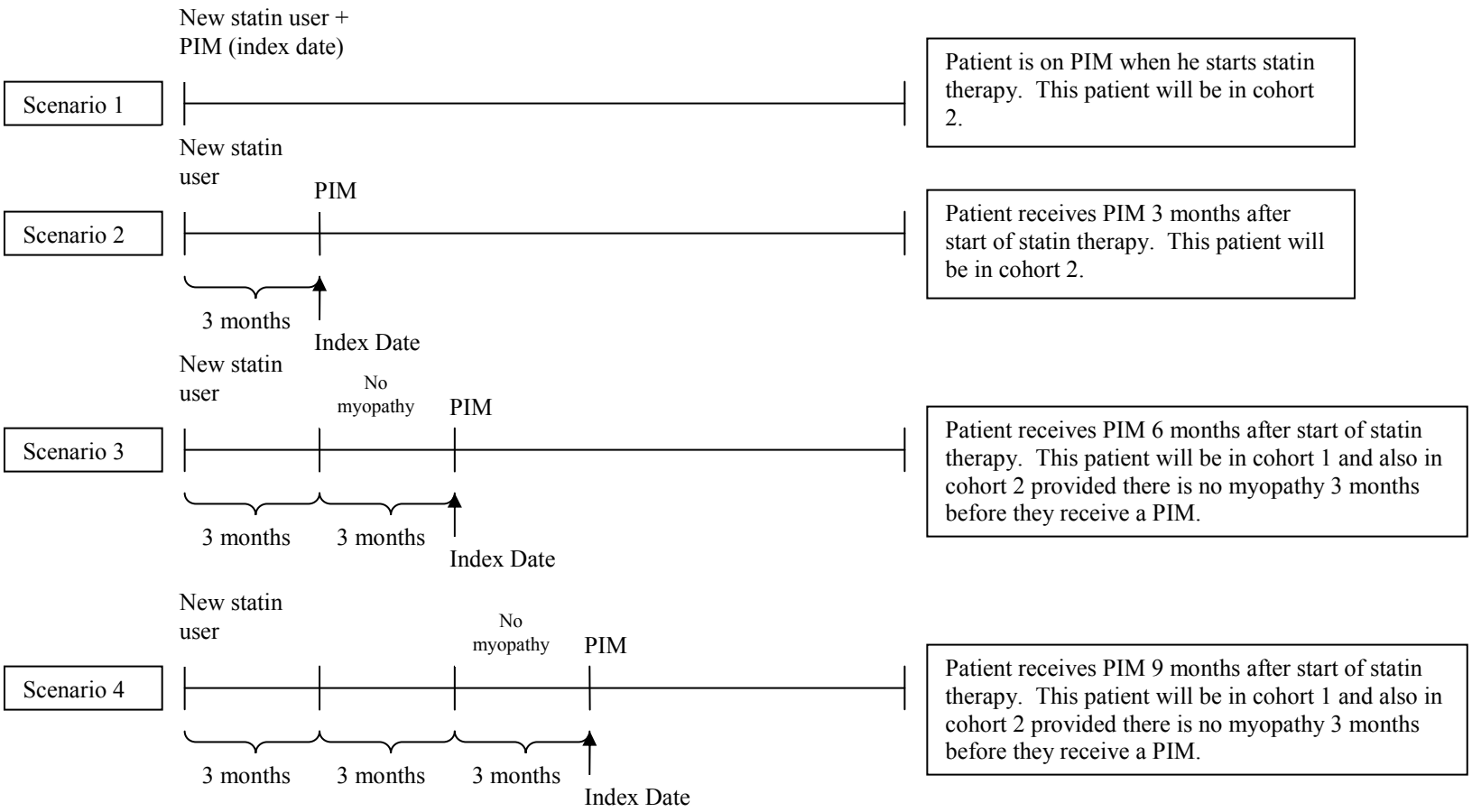
(a gap of 45 days or greater), receive a potentially interacting medication or end of the follow-up period. If a patient receives a potentially interacting medication he will then be switched to cohort 2 (i.e.the statin interacter cohort).

Thus, cohort 1 (statin users) is divided into two separate groups of patients. The first group consists of statin users who never received any potentially interacting medication throughout the study period. The second group consists of statins users who initially did not receive any potentially interacting medication but later on a potentially interacting medication was added to their therapy (at which point they changed cohorts). Thus, some of the patients in the second group will be in cohort 1 and cohort 2, which is described in detail in the next section. These two groups of patients will be kept separated and will be analyzed separately. This will be done for the ease of statistical analyses (discussed later in the statistical analyses section).

Cohort 2, the statin interacter

In this study, a patient who receives a statin drug and potentially interacting medication (as listed in Table 2.1) is defined as a statin interacter. The index date for a statin interacter will be the date statin therapy and potentially interacting medication were first received together. A PIM can be received at different time periods. Based on when a PIM was received, patients can be included in one or both cohorts. Figure 2.2 demonstrates different scenarios when a potentially interacting medication can be received and a description of the different scenarios.

Figure C.1: Description of proposed grouping of patients based on the time a PIM was received



As seen from Figure C.1, some patients are in cohort 1 and cohort 2 based on when a potentially interacting medication was received. As mentioned earlier, there should be no myopathy event three months before the index date, which for cohort two is the date the statin and potentially interacting medication was first received together. This is to be sure that the myopathy event is attributed to the concurrent use of statins and potentially interacting medications, and is not a carry-over effect from previous statin use. Statin interacters will be followed from the index date until the patients experience myopathy or discontinuation of statin therapy (a gap of 45 days or more) or PIM use or end of the follow-up period. A separate sub-group analysis will be conducted on the statin interacter groups to determine whether the risk of myopathy differs based on whether both statin and potentially interacting medication were received at the start of statin therapy or at a later date.

In summary, three multivariate analyses (discussed later) will be conducted evaluating the risk factors of myopathy. In Model 1, statin users who never received any potentially interacting medications throughout the study period will be compared with statin interacters. In Model 2, patients who initially were statin users receive potentially interacting medication and switch cohort to statin interacter group. Thus in Model 2, the same patient is being compared before and after they receive potentially interacting medication. In Model 3, only the statin interacter group will be included to evaluate the effect of time/duration of potentially interacting medication on the risk of myopathy.

Statistical Analyses

Logistic regression was used to assess the risk and risk factors of myopathy. Three separate multivariate models will be tested as mentioned earlier. In Model 1, statin users who never received any potentially interacting medications throughout the observation period will be compared with statin interacters. In Model 2, only the statin interacter group will be included to evaluate the effect of time/duration of potentially interacting medication on the risk of myopathy. For both of these models, logistic regression will be used.

In Model 2, patients who were initially statins users receive potentially interacting medication and switch to the statin interacter cohort. Thus, the same patients are being compared before and after they receive potentially interacting medications. Thus, there is correlation among observations due to the observations being made on the same patient. Logistic regression cannot be used for this model due to violation of the assumption of independence of observations. A new technique known as generalized estimating equations (GEE), which accounts for the correlation among observations, will be used for Model 2. A description of GEE is given in the next section.

Generalized Estimating Equations

Liang and Zeger[516] introduced generalized estimating equations to account for the correlation between observations in generalized linear regression models. GEE models treat the correlation structure of within-patient responses as nuisance parameters, and

[516] Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.

calculate coefficients (and corresponding SEs) using "robust" estimators. GEE models have the following characteristics: 1) can be used with continuous, binary or discrete outcomes; 2) number of observations can vary per patient; and 3) covariates can vary over time and can be continuous or categorical.[517]

GEE are marginal models, i.e., the analyst is interested in modeling the marginal expectation (average response for observations sharing the same covariates) as a function of explanatory variables.[518] The marginal regression model for binary data is:

$\text{Log}\,(E[Y_{ij}]/(1-E[Y_{ij}]) = x`_{ij}\beta$

Where $\text{Log}\,(E[Y_{ij}]/(1-E[Y_{ij}])$ = logit link which is a link function

$x`_{ij}$ = vector of study variables

β = regression parameters.

Therefore,

$$E\,(Y_{ij}) = \mu_{ij} = \frac{\exp(x`_{ij}\beta)}{1 + \exp(x`_{ij}\beta)} \text{ and}$$

$$\text{Var}\,(Y_{ij}) = V_{ij} = \frac{\exp(x`_{ij}\beta)}{[1 + \exp(x`_{ij}\beta)]^2}$$

In addition to this marginal mean model, we need to define a working correlation matrix to account for the correlated observations on a given subject. Many types of

[517] Delea T, Weycker D. *Advanced retrospective database analyses.* ISPOR 7th Annual International Meeting 2002. Washington, DC.

[518] Horton NJ, Lipsitz SR. Review of software to fit generalized estimating equation regression models. *The American Statistician* 1999;53:160-169.

correlation structures can be used for GEE.[519] In the simplest form, when all the observations are independent, the independence correlation structure is used where if ρ_{jk} is the correlation between observations j and k, $\rho_{jk} = 1$ and $\rho_{jk\,[j \neq k]} = 0$. In the case where the observations are correlated, an exchangeable correlation matrix can be used. An exchangeable correlation matrix indicates that every observation within an individual is equally correlated with every other observation in that individual. Thus, $\rho_{jj} = 1$ and $\rho_{jk\,[j \neq k]} = \rho$ where ρ is the intraclass correlation coefficient.[520]

GEE models are solved using maximum likelihood estimation. There are three assumptions of the GEE method: 1) observations for different patients are independent; 2) number of patients is large ($\geq$ 200); and 3) data must be missing completely at random.[521]

[519] Burton P, Gurrin L, Sly P. Extending the simple linear regression model to account for correlated responses: an introduction to generalized estimating equations and multi-level mixed modelling. *Stat Med* 1998;17:1261-91.
[520] Ibid.
[521] Delea T, Weycker D. *Advanced retrospective database analyses.* ISPOR 7th Annual International Meeting 2002. Washington, DC.

APPENDIX D

SENSITIVITY ANALYSIS RESULTS

A sensitivity analysis was conducted on variable duration of statin use. Duration of statin use was defined as the time a patient is exposed to statin therapy before the end of observation period. The end of observation period was defined when any one of the following three occurs: 1) diagnosis of myopathy; 2) discontinuation of statin therapy (a gap greater than 45 days between refills) or PIM use and; 3) end of six month follow-up period. In sensitivity analysis one of the criterion for end of observation period was changed. Discontinuation of statin therapy was defined as a gap of greater than 60 days between refills. Therefore duration of statin use was changed.

As a result of change in duration of statin use, the number of patients receiving PIMs during that duration also changed. A total of 8,911 patients were included in the analyses of which 5,817 patients were statin users and 3,094 were statin interacters. Objectives four, five, eight and nine were re-analyzed with this new definition of discontinuation of statin therapy and new number of total patients. The results were similar to the original results and are presented in the following section.

Objective 4: To identify demographic, health-related, treatment, and physician-related factors that are associated with the receipt of potentially interacting medications with statins.

Table D.1: Sensitivity analysis results using logistic regression to identify risk factors associated with odds of receiving a potentially interacting medication using a 60-day gap between refills

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value	Odds Ratio	95% Confidence Interval for Odds Ratio	
							Lower	Upper
Age	-0.005	0.002	5.046	1	0.025*	0.995	0.990	0.999
Gender (Female)[a]	0.422	0.047	79.963	1	<0.0001*	1.525	1.390	1.673
Ethnicity (Black)[b]	-0.095	0.060	2.462	1	0.117	0.910	0.808	1.024
Ethnicity (Hispanic)[b]	-0.281	0.055	25.845	1	<0.0001*	0.755	0.678	0.841
Ethnicity (Asian)[b]	0.059	0.155	0.146	1	0.702	1.061	0.783	1.439
Ethnicity (Other)[b]	-0.028	0.099	0.078	1	0.780	0.973	0.801	1.181
Comorbidities	0.359	0.026	192.790	1	<0.0001*	1.432	1.362	1.507
Fluvastatin[c]	-0.223	0.118	3.569	1	0.058	0.800	0.634	1.008
Atorvastatin[c]	-0.109	0.070	2.442	1	0.118	0.896	0.781	1.028
Lovastatin[c]	-0.522	0.259	4.065	1	0.044*	0.593	0.357	0.986
Simvastatin[c]	-0.189	0.077	5.725	1	0.017*	0.828	0.709	0.966
Dose of statin[d]	-0.033	0.055	0.363	1	0.547	0.967	0.869	1.077

* $p<0.05$
[a.] Reference category is male
[b.] Reference category is Whites
[c.] Reference category is pravastatin
[d.] Reference category is low dose of statin

In sensitivity analysis, the odds of receiving PIM were lower in patients receiving lovastatin than pravastatin. This was not observed in the original results.

Objective 5: To estimate the overall incidence of myopathy among study population.

Table D.2: Person-months, frequency and incidence of myopathy by statin users and statin interacters in sensitivity analysis using 60-day gap between refills

	Statin Users	**Statin Interacters**
n	5,817	3,094
Follow-up in person-months	24,263	14,746
Myopathy (%)	49 (0.8)	67 (2.1)
Incidence[a]	0.20	0.45

a. New myopathy cases per 100 person-months

Objective 8: To assess the relationship between the development of myopathy and use of potentially interacting medications with statins, while controlling for other risk factors for myopathy.

Table D.3: Sensitivity analysis results using logistic regression to assess the relationship between odds of developing myopathy and use of potentially interacting medications using 60-day gap between refills

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value	Odds Ratio	95% Confidence Interval for Odds Ratio	
							Lower	Upper
Receipt of PIM[a]	1.042	0.198	27.618	1	<0.0001*	2.835	1.922	4.181
Age	0.012	0.010	1.302	1	0.254	1.012	0.992	1.033
Gender (Female)[b]	0.307	0.204	2.267	1	0.132	1.359	0.912	2.026
Ethnicity (Black)[c]	-0.379	0.258	2.162	1	0.141	0.684	0.413	1.135
Ethnicity (Hispanic)[c]	-0.289	0.227	1.626	1	0.202	0.748	0.480	1.168
Ethnicity (Other)[c]	-0.570	0.407	1.961	1	0.161	0.566	0.255	1.256
Diabetes[d]	0.157	0.192	0.667	1	0.414	1.170	0.802	1.708
Comorbidities	0.189	0.058	10.664	1	0.001*	1.209	1.079	1.354
Atorvastatin[e]	0.288	0.301	0.916	1	0.338	1.334	0.739	2.407
Simvastatin[e]	0.122	0.339	0.129	1	0.719	1.130	0.582	2.194
Other statins[e]	-1.111	0.759	2.143	1	0.143	0.329	0.074	1.457
Duration of statin use	-0.002	0.000	8.922	1	0.003*	0.998	0.996	0.999
Dose of statin[f]	-0.190	0.226	0.709	1	0.399	0.827	0.531	1.288

* $p<0.05$
[a.] PIM – Potentially interacting medication
[b.] Reference category is male
[c.] Reference category is Whites
[d.] Reference category is absence of diabetes
[e.] Reference category is pravastatin
[f.] Reference category is low doses of statin

Objective 9: To determine the risk factors (demographic factors, health risk factors, and treatment factors) for myopathy.

Table D.4: Sensitivity analysis results using logistic regression to determine the risk factors of myopathy using 60-day gap between refills

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value	Odds Ratio	95% Confidence Interval for Odds Ratio	
							Lower	Upper
Receipt of PIM[a]	1.042	0.198	27.618	1	<0.0001*	2.835	1.922	4.181
Age	0.012	0.010	1.302	1	0.254	1.012	0.992	1.033
Gender (Female)[b]	0.307	0.204	2.267	1	0.132	1.359	0.912	2.026
Ethnicity (Black)[c]	-0.379	0.258	2.162	1	0.141	0.684	0.413	1.135
Ethnicity (Hispanic)[c]	-0.289	0.227	1.626	1	0.202	0.748	0.480	1.168
Ethnicity (Other)[c]	-0.570	0.407	1.961	1	0.161	0.566	0.255	1.256
Diabetes[d]	0.157	0.192	0.667	1	0.414	1.170	0.802	1.708
Comorbidities	0.189	0.058	10.664	1	0.001*	1.209	1.079	1.354
Atorvastatin[e]	0.288	0.301	0.916	1	0.338	1.334	0.739	2.407
Simvastatin[e]	0.122	0.339	0.129	1	0.719	1.130	0.582	2.194
Other statins[e]	-1.111	0.759	2.143	1	0.143	0.329	0.074	1.457
Duration of statin use	-0.002	0.000	8.922	1	0.003*	0.998	0.996	0.999
Dose of statin[f]	-0.190	0.226	0.709	1	0.399	0.827	0.531	1.288

* $p<0.05$
[a.] PIM – Potentially interacting medication
[b.] Reference category is male
[c.] Reference category is Whites
[d.] Reference category is absence of diabetes
[e.] Reference category is pravastatin
[f.] Reference category is low doses of statin

Table D.5: Sensitivity analysis results using logistic regression to determine PIM characteristics that are risk factors for myopathy for statin interacters suing 60-day gap between refills

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value	Odds Ratio	95% Confidence Interval for Odds Ratio	
							Lower	Upper
Age	0.037	0.015	6.124	1	0.013*	1.038	1.008	1.069
Gender (Female)[a]	0.077	0.273	0.081	1	0.776	1.081	0.632	1.848
Ethnicity (Black)[b]	-0.253	0.342	0.546	1	0.459	0.777	0.397	1.518
Ethnicity (Hispanic)[b]	-0.106	0.305	0.122	1	0.727	0.899	0.495	1.634
Ethnicity (Other)[b]	-0.395	0.492	0.643	1	0.422	0.673	0.256	1.770
Diabetes[c]	0.080	0.254	0.101	1	0.751	1.084	0.658	1.787
Comorbidities	0.138	0.066	4.305	1	0.038*	1.148	1.008	1.308
Atorvastatin[d]	0.315	0.399	0.622	1	0.430	1.371	0.626	3.002
Simvastatin[d]	0.458	0.435	1.106	1	0.293	1.581	0.674	3.711
Other statins[d]	-1.145	1.066	1.153	1	0.282	0.318	0.039	2.572
Duration of statin use	-0.001	0.000	3.074	1	0.079	0.999	0.997	1.000
Dose of statin[e]	-0.479	0.321	2.227	1	0.135	0.619	0.330	1.162
Significance of drug interaction								
Level 2[f]	-0.196	0.298	0.432	1	0.511	0.822	0.458	1.475
Level 3[f]	-1.107	1.033	1.147	1	0.284	0.330	0.044	2.506
Time of receipt of PIM[g, h]	0.303	0.342	0.7844	1	0.376	1.354	0.692	2.648
Duration of PIM[h] use	-0.003	0.002	1.805	1	0.179	0.330	0.044	2.506

* $p<0.05$
[a.] Reference category is male
[b.] Reference category is Whites
[c.] Reference category is absence of diabetes
[d.] Reference category is pravastatin
[e.] Reference category is low doses of statin
[f.] Reference category is Level 1
[g.] Reference category is PIM received after start of statin therapy
[h.] PIM – Potentially interacting medication

APPENDIX E

RESULTS OF NORMALITY TESTING

Normality plots and tests were conducted for continuous variables age, duration of statin use, and duration of PIM use. Table E.1 provide information on skewness and kurtosis. Figures E.1 to E.3 show the normality plots for the three variables

Table E.1: Skewness and kurtosis for age, duration of statin use and duration of PIM use

Variables	Skewness (S.E.)	Kurtosis (S.E.)
Age	-0.822 (0.026)	-0.017 (0.52)
Duration of statin use	3.668 (0.026)	21.685 (0.052)
Duration of PIM use	0.944 (0.045)	-0.674 (0.089)

Figure E.1: Normality plot for age

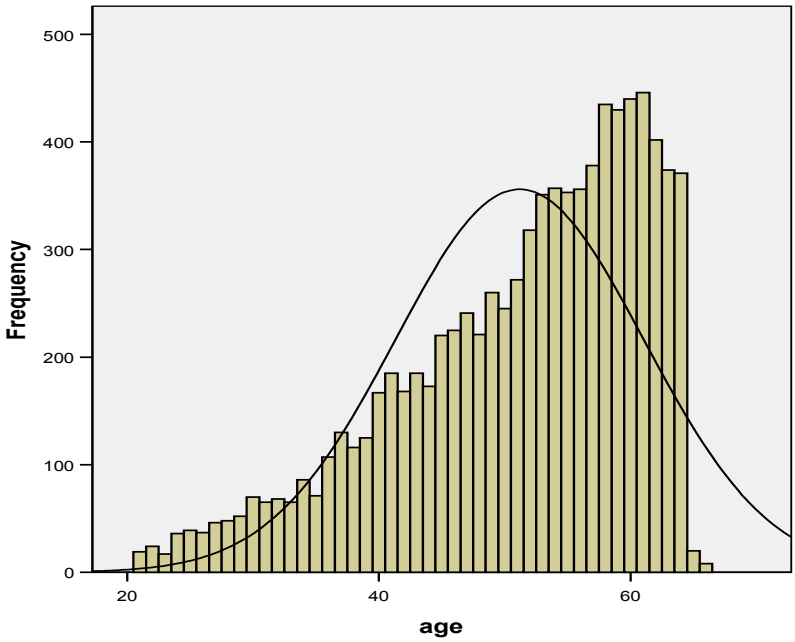


Figure E.2: Normality plot for duration of statin use

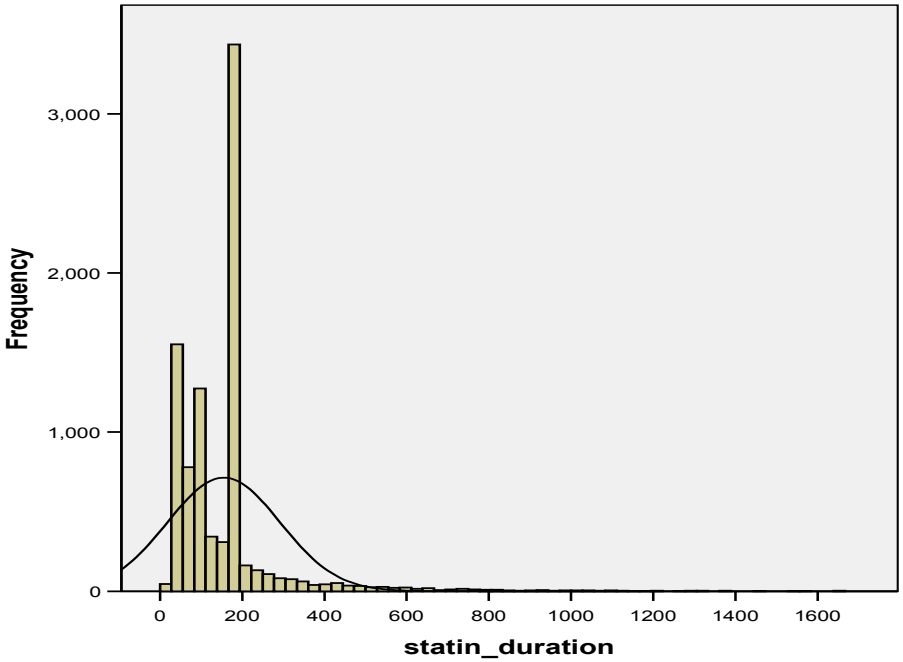
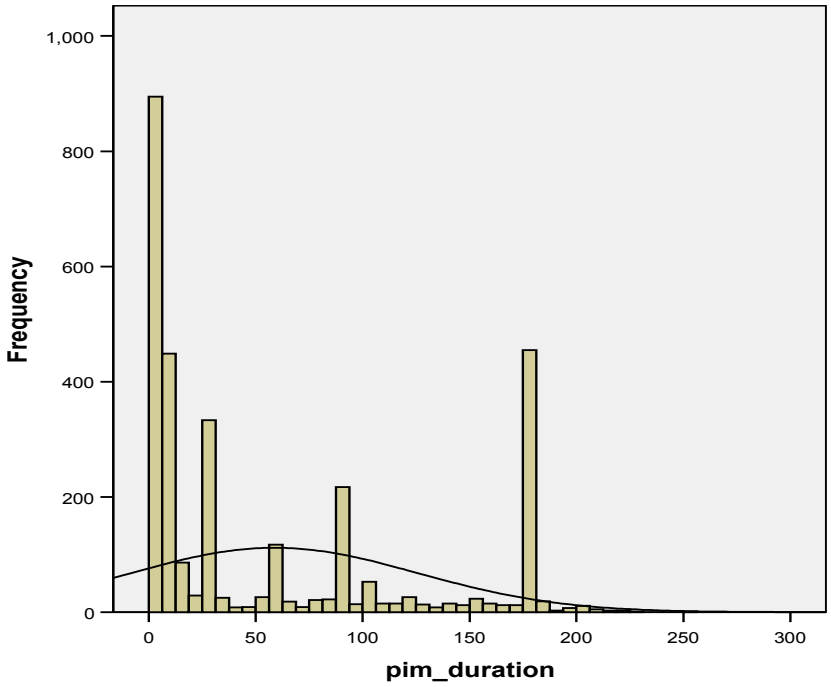


Figure E.3: Normality plot for duration of PIM use



APPENDIX F

RESULTS OF TESTING ASSUMPTIONS OF LOGISTIC REGRESSION ANALYSES

LINEARITY AMONG PREDICTORS

Table F.1: Results of Box-Tidwell approach to test linearity among predictors for logistic regression model that identifies risk factors associated with odds of receiving a potentially interacting medication

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value
Age	0.156	0.088	3.128	1	0.077
Gender (Female)[a]	0.429	0.047	81.234	1	<0.0001
Ethnicity (Black)[b]	-0.083	0.060	1.894	1	0.168
Ethnicity (Hispanic)[b]	-0.278	0.055	24.832	1	<0.001
Ethnicity (Asian)[b]	0.109	0.155	0.496	1	0.481
Ethnicity (Other)[b]	0.013	0.099	0.019	1	0.889
Comorbidities	0.355	0.026	183.155	1	<0.0001
Fluvastatin[c]	-0.222	0.119	3.488	1	0.061
Atorvastatin[c]	-0.1135	0.079	2.565	1	0.109
Lovastatin[c]	-0.496	0.258	3.683	1	0.055
Simvastatin[c]	-0.186	0.079	5.505	1	0.019
Dose of statin[d]	-0.034	0.055	0.385	1	0.534
Age*Log(Age)	-0.033	0.018	3.349	1	0.067

[a.] Reference category is male
[b.] Reference category is Whites
[c.] Reference category is pravastatin
[d.] Reference category is low dose of statin

Table F.2: Results of Box-Tidwell approach to test linearity among predictors for logistic regression model that evaluates risk factors associated with odds of developing myopathy

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value
Receipt of PIM[a]	1.023	0.201	25.761	1	<0.0001
Age	-0.255	0.371	0.472	1	0.491
Gender (Female)[b]	0.263	0.205	1.645	1	0.199
Ethnicity (Black)[c]	-0.403	0.264	2.330	1	0.126
Ethnicity (Hispanic)[c]	-0.252	0.231	1.191	1	0.275
Ethnicity (Other)[c]	-0.526	0.409	1.658	1	0.197
Diabetes[d]	0.168	0.197	0.733	1	0.391
Comorbidities	0.322	0.089	13.026	1	0.000
Atorvastatin[e]	0.276	0.302	0.835	1	0.360
Simvastatin[e]	0.073	0.341	0.045	1	0.830
Other statins[e]	-1.139	0.760	2.244	1	0.134
Duration of statin use	-0.024	0.006	13.969	1	0.000
Dose of statin[f]	-0.154	0.228	0.455	1	0.499
age*log (age)	0.054	0.076	0.509	1	0.475
Duration of statin use* log (Duration of statin)	-0.221	0.119	3.450	1	0.063

[a.] PIM – Potentially interacting medication
[b.] Reference category is male
[c.] Reference category is Whites
[d.] Reference category is absence of diabetes
[e.] Reference category is pravastatin
[f.] Reference category is low doses of statin

Table F.3: Results of Box-Tidwell approach to test linearity among predictors for logistic regression model that evaluates PIM characteristics associated with odds of developing myopathy

Variable	Parameter Estimate	Standard Error	Wald χ^2	df	p-value
Age	-0.768	0.520	2.175	1	0.140
Gender (Female)[a]	0.100	0.278	0.130	1	0.717
Ethnicity (Black)[b]	-0.164	0.358	0.209	1	0.647
Ethnicity (Hispanic)[b]	0.023	0.312	0.005	1	0.940
Ethnicity (Other)[b]	-0.310	0.498	0.388	1	0.533
Diabetes[c]	0.053	0.265	0.041	1	0.839
Comorbidities	0.310	0.113	7.462	1	0.006
Atorvastatin[d]	0.296	0.404	0.535	1	0.464
Simvastatin[d]	0.4217	0.4426	0.9077	1	0.340
Other statins[d]	-1.094	1.069	1.049	1	0.305
Duration of statin use	0.0009	0.010	0.008	1	0.928
Dose of statin[e]	-0.468	0.325	2.063	1	0.150
Significance of drug interaction					
Level 2[f, g]	-0.421	0.306	1.886	1	0.169
Level 3[f, h]	-1.534	1.036	2.190	1	0.138
Time of receipt of PIM[i, j]	0.093	0.333	0.078	1	0.779
Duration of PIM[j] use	0.098	0.033	8.507	1	0.003
age*log (age)	0.164	0.107	2.355	1	0.124
duration of statin use*log (duration of statin use)	-0.0003	0.001	0.040	1	0.841
Duration of PIM use*log (duration of PIM use)	0.073	0.341	0.045	1	0.830

[a.] Reference category is male
[b.] Reference category is Whites
[c.] Reference category is absence of diabetes
[d.] Reference category is pravastatin
[e.] Reference category is low doses of statin
[f.] Reference category is Level 1 which is defined as severe or potentially life-threatening.
[g.] Level 2 is defined as interaction that causes detoriation in patients' clinical status.
[h.] Level 3 is defined as moderate to minor side effects.
[i.] Reference category is PIM received after start of statin therapy
[j.] PIM – Potentially interacting medication

MULTICOLLINEARITY

Table F.4: Tolerance and variance inflation factor to test multicollinearity for logistic regression model that identifies risk factors associated with odds of receiving a potentially interacting medication

Variable	df	Tolerance	Variance Inflation Factor
Age	1	0.946	1.056
Gender (Female)	1	0.980	1.020
Ethnicity (Black)	1	0.804	1.242
Ethnicity (Hispanic)	1	0.795	1.257
Ethnicity (Asian)	1	0.957	1.044
Ethnicity (Other)	1	0.909	1.099
Comorbidities	1	0.953	1.049
Fluvastatin	1	0.749	1.334
Atorvastatin	1	0.409	2.439
Lovastatin	1	0.939	1.064
Simvastatin	1	0.431	2.318
Dose of statin	1	0.916	1.090

Table F.5: Tolerance and variance inflation factor to test multicollinearity for logistic regression model that evaluates risk factors associated with odds of developing myopathy

Variable	df	Tolerance	Variance Inflation Factor
Receipt of PIM	1	0.851	1.174
Age	1	0.927	1.078
Gender (Female)	1	0.965	1.035
Ethnicity (Black)	1	0.798	1.251
Ethnicity (Hispanic)	1	0.772	1.294
Ethnicity (Other)	1	0.882	1.132
Diabetes	1	0.948	1.054
Comorbidities	1	0.930	1.075
Atorvastatin	1	0.409	2.443
Simvastatin	1	0.430	2.321
Other statins	1	0.719	1.390
Duration of statin use	1	0.859	1.163
Dose of statin	1	0.915	1.092

Table F.6: Tolerance and variance inflation factor to test multicollinearity for logistic regression model that evaluates PIM characteristics associated with odds of developing myopathy

Variable	df	Tolerance	Variance Inflation Factor
Age	1	0.90308	1.10732
Gender (Female)	1	0.93351	1.07122
Ethnicity (Black)	1	0.80737	1.23858
Ethnicity (Hispanic)	1	0.78998	1.26586
Ethnicity (Other)	1	0.88512	1.12979
Diabetes	1	0.94643	1.05660
Comorbidities	1	0.93399	1.07067
Atorvastatin	1	0.43195	2.31509
Simvastatin	1	0.45557	2.19504
Other statins	1	0.75491	1.32465
Duration of statin use	1	0.87476	1.14317
Dose of statin	1	0.90597	1.10379
Significance of drug interaction			
Level 2	1	0.73700	1.35686
Level 3	1	0.89695	1.11489
Time of receipt of PIM	1	0.67782	1.47532
Duration of PIM use	1	0.59675	1.67574

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